The Journal of
HEREDITY

WARNING!

". . . like most species, we are already encumbered by countless undesirable mutations, from which no individual is immune. In this situation we can, however, draw the practical lesson, from the fact of the great majorty of mutations being undesirable, that their further random production in ourselves should so far as possible be rigorously avoided. As we can infer with certainty from experiments on lower organisms that all high-energy radiation must produce such mutations in man, it becomes an obligation for radiologists—though one far too little observed as yet in most countries—to insist that the simple precautions are taken which are necessary for shielding the gonads, whenever people are exposed to such radiation, either in industry or in medical practice. And, with the coming increasing use of atomic energy, even for peace-time purposes, the problem will become very important of insuring that the human germ plasm—the all-important material of which we are the temporary custodians—is effectively protected from this additional and potent source of permanent contamination."

—H. J. Muller.

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The American Genetic Association

An incorporated organization devoted to promoting a knowledge of the laws of heredity and their application to the improvement of plants, animals, and human racial stocks

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Nobel Laureate

TWIN NEEDS OF SCIENCE

WE scientists feel as if we have a little glimpse into the millenium when we visit Sweden and see what encouragements and what a high place of honor are accorded to the scientific way of life in your country. The institution of the Nobel awards is the most outstanding expression of this spirit, and it serves most effectively in spreading it wide and deep throughout the world. And, like the other recipients of the award here today, I for one am personally moved most profoundly in being chosen as one vehicle in the transmission of this great service.

An important part of the insight of Nobel lay in the fact that he did not try to separate the seeking after fundamental truths from the seeking of benefits for mankind. In some scientific work one, in others the other aspect may be more apparent, but in fact they are closely interdependent, and only the dual recognition can provide a basis for the richest, fullest and most effective motivation on the part of a scientist. We would however be hypocrites if we were to pretend today that the increase of knowledge in any particular field inevitably leads to human betterment. The example of the power of Nobel's invention, dynamite, for good OR ill is as everyone knows far outmoded nowadays by modern physical, chemical and biological means of metamorphosing the structure of inanimate and animate matter. And scientists can no longer stand aloof from the question of whether their work will be used to wreck or re-create civilization, even though they can scarcely have the deciding voice.

But most of us scientists, I hope, have come to know that, both for the further expansion of human understanding and human control over nature, and also for the increase of our general human well-being—in fact, for the very saving of us from destruction—there are today two great underlying requirements. One is that the thousands-of-years-old growth (ofttimes very painful) in the freedom of the human spirit to examine into and question all things, and to communicate one's thoughts, doubts, findings and criticisms freely in every field, should go on, and should be greatly accelerated, and spread to all the peoples of the earth. This means a society of men educated in all the fundamentals of modern knowledge, and trained to think independently and fearlessly. But, to be effective, it means, secondly, the bringing of the benefits of modern techniques to all, the raising of the standard of living of the broad masses everywhere, not exclusive of any groups or races, as they could now be raised with the aid of modern science, so as to make high culture and free criticism not the unstable possession of a limited sector of society, as among the ancient Greeks, but a part of the accepted inheritance of all humanity. This implies among other things not only suitable employment for all but also a more effective, more informed, and more direct participation than exists in most places, on the part of what are now the fourth and fifth estates, in the making of decisions affecting themselves and the commonalty. For human nature has never proved altruistic enough to allow the interests of one group to be successfully entrusted to another one. Necessarily this will require some sacrifice on the part of some of those now more favored, but it will be to the benefit of their children too in the end.

History indicates the suppression of either one of these two related modes of progress to be equally disastrous. In fact, the destruction of civilization, and of most of mankind, today, would hardly be more deplorable than the sealing of the bonds of either our intellectual or our economic enslavement by the victory, even if bloodless, of any system which, though it temporarily offered one of these two types of development, gave no hope for progress in the other.

It is to be fervently hoped that the world will have to make no such devil's choice. In the quantitatively major countries many scientific men, especially among the physicists, are coming to realize the urgency of this matter, and so are many publicists and many ordinary people, but not nearly enough of them yet. Sweden, however, is one of the few countries which is very notable in having made great advances in the simultaneous solution of the problems involved in both required lines of development, and the example of Sweden is most heartening to all the world. With a background of such progress here in both directions, the nourishment which this country gives to science, and which is so well represented in the institution of the Nobel awards, may be expected here at least to redound to mankind's benefit only. Could this be true of other countries as well, we might look forward with enthusiasm to the future.

But we of the other countries must not allow our efforts to be frustrated by the greater complexity and size of our own problems. In particular, it is the obligation of scientists in all fields to do what they can to bring to people's minds that better realization of the situation which should come from knowledge of the possibilities of science for good and for bad, and from knowledge of the requirements of science, and of the ultimate dependence of scientific development on general human development. The institution founded by Nobel is a most powerful force in helping to give scientists the necessary voice for this, as well as in making them more cognizant of their heavy responsibilities in this regard. And the fact that the main seat of this institution is in Sweden is an extremely fortunate circumstance, in helping to put forward that blazing ideal towards which scientists, in common with all humanity, must now more than ever strive with all their might.—**H. J. MULLER.**

(Speech given at the Nobel banquet, Stockholm, December 10, 1946.)

te *In Sweden*

THE PRODUCTION OF MUTATIONS*

IF, as Darwin maintained, the adaptiveness of living things results from natural selection, rather than from a teleological tendency in the process of variation itself, then heritable variations must, under most conditions, occur in numerous directions, so as to give a wide range of choice for the selective process. Such a state of affairs seems, however, in more or less contradiction to the commonly held idea, to which Darwin also gave some credence, that heritable variations of given kinds tend to be produced, in a fairly regular way, by given kinds of external conditions. For then we are again confronted with the difficulty, how is it that the "right kinds" of variations (*i.e.* the adaptive ones) manage to arise in response to the "right kinds" of conditions (*i.e.* those they are adapted to)? Moreover, the de Vriesian notion of mutations does not help us in this connection. On that view, there are sudden jumps, going all the way from one "elementary species" to another, and involving radical changes in numerous characters at once, and there are relatively few different jumps to choose between. This obviously would fail to explain how, through such coarse steps, the body could have come to be so remarkably streamlined in its internal and external organization, or, in other words, so thoroughly adaptive.

The older selectionists, thinking in terms of chemical reactions on a molar scale when they thought in terms of chemistry at all, did not realize sufficiently the ultramicroscopic randomness of the processes causing inherited variations. The earliest mutationists failed, in addition, to appreciate the qualitative and quantitative multiplicity of mutations. It was not long, however, before the results of Baur on *Antirrhinum* and of Morgan on *Drosophila*, supplemented by scattered observations on other forms, gave evidence of the occurrence of numerous Mendelizing mutations, many of them small ones, in varied directions, and they showed no discoverable relation between the type of mutation and the type of environment or condition of living under which it arose. These observations, then, came closer to the statistical requirements for a process of evolution which has its basis in accidents. In what sense, however, could the events be regarded as accidental? Were they perhaps expressions of veiled forces working in a more determinate manner? It was more than ever evident that further investigation of the manner of occurrence of mutations was called for.

If the mutations were really non-teleological, with no relation between type of environment and type of change, and above all no adaptive relation, and if they were of as numerous types as the theory of natural selection would demand, then the great majority of the changes should be harmful in their effects, just as any alterations made blindly in a complicated apparatus are usually detrimental to its proper functioning, and many of the larger changes should even be totally incompatible with the functioning of the whole, or, as we say, lethal. That is, strange as it may seem at first sight, we should expect most mutations to be disadvantageous if the theory of natural selection is correct. We should also expect these mainly disadvantageous changes to be highly diversified in their genetic basis.

Frequency of Mutations

To get exact evidence on these points required the elaboration of special genet-

*Nobel Prize lecture delivered by Dr. H. J. Muller before the Caroline Institute, Stockholm, Sweden, December 12, 1946.

ic methods, adapted to the recognition of mutations that ordinarily escape detection—(1) lethals, (2) changes with but small visible effects, and (3) changes without any externally visible effects but influencing the viability more or less unfavorably. It would take us too far afield to explain these techniques here. Suffice it to say that they made use of the principle according to which a chromosome is, as we say, "marked," by having had inserted into it to begin with one or more known mutant genes with conspicuous visible effects, to differentiate it from the homologous chromosome. An individual with two such differentiated chromosomes, when appropriately bred, will then be expected to give two groups of visibly different offspring, holding certain expected ratios to one another. If, however, a lethal mutation has occurred in one of the two chromosomes, its existence will be made evident by the absence of the corresponding expected group of offspring. Similarly, a mutated gene with invisible but somewhat detrimental action, though not fully lethal, will be recognized by the fact that the corresponding group of offspring are found in smaller numbers than expected. And a gene with a very small visible effect, that might be overlooked in a single individual, will have a greatly increased chance of being seen because the given group of offspring as a whole will tend to be distinguished in this regard from the corresponding group derived from a non-mutant.

In this way, it was possible in the first tests of this kind, which Altenburg and the writer conducted, partly in collaboration, in 1918-19, to get definite evidence in *Drosophila* that the lethal mutations greatly outnumbered those with visible effects, and that among the latter the types having an obscure manifestation were more numerous than the definite conspicuous ones used in ordinary genetic work. Visible or not, the great majority had lowered viability. Tests of their genetic basis, using the newly found facts of linkage, showed them to be most varied in their locus in the chromosomes, and it could be calculated by a simple extrapolative process that there must be at least hundreds, and probably thousands, of different kinds arising in the course of spontaneous mutation. In work done much later, employing induced mutations, it was also shown (in independent experiments both of the present writer and Kerkis, and of Timoféeff and his co-workers, done in 1934) that "invisible" mutations, which by reason of one or another physiological change lower viability without being fully lethal, form the most abundant group of any detected thus far, being at least two to three times as numerous as the complete lethals. No doubt there are in addition very many, perhaps even more, with effects too small to have been detected at all by our rather crude methods. It is among these that we should be most apt to find those rare accidents which, under given conditions or in given combinations with others, may happen to have some adaptive value. Tests of Timoféeff, however, have shown that even a few of the more conspicuous visible mutations do in certain combinations give an advantage in laboratory breeding.

Because of the nature of the test whereby it is detected—the absence of an entire group of offspring bearing certain conspicuous expected characters—a lethal is surer of being detected, and detected by any observer, than is the inconspicuous or invisible, merely detrimental, mutation. Fortunately, there are relatively few borderline cases, of nearly but not quite completely lethal genes. It was this objectivity of recognition, combined with the fact that they were so much more numerous than conspicuous visible mutations, that made it feasible for lethals to be used as an index of mutation frequency, even though they suffer from the disadvantage of requiring the breeding of an individual, rather than its mere inspection, for the recognition that it carries a lethal. In the earliest published work, we (Altenburg and the author) attempted not only to find a quantitative value for the "normal" mutation frequency, but also to determine whether a certain condition, which we

considered of especial interest, affected the mutation frequency. The plan was ultimately to use the method as a general one for studying the effects of various conditions. The condition chosen for the first experiment was temperature, and the results, verified by later work of the writer's, indicated that a rise of temperature, within limits normal to the organism, produced an increase of mutation frequency of about the amount to be expected if mutations were, in essentials, orthodox chemical reactions.

Mutations as Chemical Reactions

On this view, however, single mutations correspond with individual molecular changes, and an extended series of mutations, in a great number of identical genes in a population, spread out over thousands of years, is what corresponds with the course of an ordinary chemical reaction that takes place in a whole collection of molecules in a test tube in the course of a fraction of a second or a few seconds. For the individual gene, in its biological setting, is far more stable than the ordinary chemical molecule is, when the latter is exposed to a reagent in the laboratory. Thus, mutations, when taken collectively, should be subject to the statistical laws applying to mass reactions, but the individual mutation, corresponding to a change in one molecule, should be subject to the vicissitudes of ultramicroscopic or atomic events, and the apparition of a mutant individual represents an enormous amplification of such a phenomenon. This is a principle which gives the clue to the fact, which otherwise seems opposed to a rational, scientific and molarly deterministic point of view, that differences in external conditions or conditions of living do not appear to affect the occurrence of mutations, while on the other hand, even in a normal and sensibly constant environment, mutations of varied kinds do occur. It is also in harmony with our finding, of about the same time, that when a mutation takes place in a given gene, the other gene of identical type present nearby in the same cell usually remains unaffected though it must of course have been subjected to the same macroscopic physicochemical conditions. On this conception, then, the mutations ordinarily result from submicroscopic accidents, that is, from caprices of thermal agitation, that occur on a molecular and submolecular scale. More recently Delbrück and Timoféeff, in more extended work on temperature, have shown that the amount of increase in mutation frequency with rising temperature is not merely that of an ordinary test-tube chemical reaction, but in fact corresponds closely with that larger rise to be expected of a reaction as slow in absolute time rate (*i.e.* with as small a proportion of molecular changes per unit of time) as the observed mutation frequency shows this reaction to be, and this quantitative correspondence helps to confirm the entire conception.

Now this inference concerning the non-molar nature of the individual mutation process, which sets it in so different a class from most other grossly observable chemical changes in nature, led naturally to the expectation that some of the "point effects" brought about by high-energy radiation like X-rays would also work to produce alternations in the hereditary material. For if even the relatively mild events of thermal agitation can, some of them, have such consequences, surely the energetically far more potent changes caused by powerful radiation should succeed. And, as a matter of fact, our trials of X-rays, carried out with the same kind of genetic methods as previously used for temperature, proved that such radiation is extremely effective, and inordinately more so than a mere temperature rise, since by this method it was possible to obtain, by a half hour's treatment, over a hundred times as many mutations in a group of treated cells as would have occurred in them spontaneously in the course of a whole generation. These mutations, too, were found ordinarily to occur pointwise and randomly, in one gene at a time, without affecting an identical

gene that might be present nearby in a homologous chromosome.

Radiation-Effects

In addition to the individual gene changes, radiation also produced rearrangements of parts of chromosomes. As our later work (including that with co-workers, especially Raychaudhuri and Pontecorvo) has shown, these latter were caused in the first place by breakages of the chromosomes, followed afterwards by attachments occurring between the adhesive broken ends, that joined them in a different order than before. The two or more breaks involved in such a rearrangement may be far apart, caused by independent hits, and thus result in what we call a *gross* structural change. Such changes are of various kinds, depending upon just where the breaks are and just w' ich broken ends become attached to which. But, though the effects of the individual "hits" are rather narrowly localized, it is not uncommon for two breaks to be produced at nearby points by what amounts to one local change (or at any rate one localized group of changes) whose influence becomes somewhat spread out. By the rejoining, in a new order, of broken ends resulting from two such nearby breaks, a *minute* change of sequence of the genes is brought about. More usually, the small piece between the two breaks becomes lost (a "deficiency"), but sometimes it becomes inverted, or even becomes transferred into a totally different position, made available by a separate hit.

Both earlier and later work by collaborators (Oliver, Hanson, etc.) showed definitely that the frequency of the gene mutations is directly and simply proportional to the dose of irradiation applied, and this despite the wave length used, whether X- or gamma or even beta rays, and despite the timing of the irradiation. These facts have since been established with great exactitude and detail, more especially by Timoféeff and his co-workers. In our more recent work with Raychaudhuri these principles have been extended to total doses as low as 400*r*, and rates as low as .01*r* per minute, with gamma rays. They leave, we believe, no escape from the conclusion that there is no threshold dose, and that the individual mutations result from individual "hits", producing genetic effects in their immediate neighborhood. Whether these so-called "hits" are the individual ionizations, or may even be the activations that occur at lower energy levels, or whether, at the other end of the scale, they require the clustering of ionizations that occurs at the termini of electron tracks and of their side branches (as Lea and Fano point out might be the case), is as yet undecided. But in any case they are, even when microscopically considered, what we have termed "point mutations," as they involve only disturbances on an ultramicroscopically localized scale. And whether or not they are to occur at any particular point is entirely a matter of accident, using this term in the sense in which it is employed in the mathematics of statistics.

Naturally, other agents than photons which produce effects of this kind must also produce mutations, as has been shown by students and collaborators working under Altenburg in Houston for neutrons (Nagai and Locher) and for alpha rays (Ward) and confirmed by Timoféeff and his co-workers (Zimmer, et al). Moreover, as Altenburg showed, even the smaller quantum changes induced by ultraviolet exert this effect on the genes. They cause, however, only a relatively small amount of rearrangement of chromosome parts (Muller and Mackenzie), and, in fact, they also tend to inhibit such rearrangement, as Swanson, followed by Kauffmann and Hollaender, has found. Since the effective ultraviolet hits are in the form of randomly scattered single-atom changes in the purines and pyrimidines of the chromosome, rather than in groups of atom changes, it seems likely that clusters of ionizations are not necessary for the gene mutation effects, at any rate, although we cannot be sure of this until the relation of mutation frequency to dosage is better known for this agent.

Induced and Natural Mutations

Inasmuch as the changes brought about in the genes by radiation must certainly be of an accidental nature, unpremeditated, ateleological, without reference to the value of the end result for the organism or its descendants, it is of interest to compare them with the so-called spontaneous or natural mutations. For in the radiation mutations we have a yardstick of what really random changes should be. Now it is found in *Drosophila* that the radiation-induced mutations of the genes (we exclude here the demonstrable chromosome rearrangements) are in every respect which has been investigated of the same essential nature as those arising naturally in the laboratory or field. They usually occur in one gene without affecting an identical one nearby. They are distributed similarly in the chromosomes. The effects, similarly, may be large or small and there is a similar ratio of fully lethal to so-called visible gene mutations. That is, the radiation mutations of the genes do not give evidence of being more deleterious. And when one concentrates attention upon given genes one finds that a whole series of different forms, or alleles, may be produced, of a similar and in many cases sensibly identical nature in the two cases. In fact, every natural mutation, when searched for long enough, is found to be producible also by radiation. Moreover, under any given condition of living tried, without radiation, the effects appear as scattered as when radiation is applied, even though of much lower frequency. All this surely means then, does it not, that the natural mutations have in truth no innate tendency to be adaptive, nor even to be different, as a whole group, under some natural conditions than under others? In other words, they cannot be determinate in a molar sense, but must themselves be caused by the ultramicroscopic accidents of the molecular and submolecular motions, *i.e.* by the individual quantum exchanges of thermal agitation, taking this word in a broad sense. The only escape from this would be to suppose that they are caused by the radiation present in nature, resulting from natural radioactive substances and cosmic rays, but a little calculation (by Mott-Smith and the writer, corroborated by others) has shown that this radiation is quite inadequate in amount to account for the majority of mutations occurring in most organisms.

But to say that most natural mutations are the results of the quantum exchanges of thermal agitation, and, further, that a given energy level must be reached to produce them, does not, as some authors have seemed to imply, mean that the physicochemical conditions in and around the organism, other than temperature, have no influence upon their chance of occurrence. That such circumstances may play a decided role was early evident from the studies of spontaneous mutation frequency, when it was found (1921, reported 1928) that the frequency in one experiment, with one genetic stock, might be ten times as high as in another, with another stock. And more recently we have found that, in different portions of the natural life cycle of the same individual, the mutation frequency may be very different. Finally, in the work of Auerbach and Robson, with mustard gas and related substances, it has been proved that these chemicals may induce mutations at as high a frequency as a heavy dose of X-rays. In all these cases, however, the effects are similarly scattered at random, individually uncontrolled, and similarly non-adaptive.

It should also be noted in this connection that the genes are not under all conditions equally vulnerable to the mutating effects of X-rays themselves. Genes in the condensed chromosomes of spermatozoa, for example, appear to be changed more easily than those in the more usual "resting" stages. We have mentioned that, as Swanson has shown, ultraviolet exerts besides its own mutating effect an inhibition on the process of chromosome breakage, or at any rate on that of reunion of the broken parts in a new viable order, while infrared, in Hollaender's and Kaufmann's recent experi-

ments, has a contrary action. And Stadler, in his great work on the production of mutations in cereals, started independently of our own, has obtained evidence that in this material X-radiation in the doses used is unable to produce a sensible rise in the gene mutation frequency, though numerous chromosome breakages do arise, leading to both gross and minute rearrangements of chromosome parts. Either the genes are more resistant in this material to permanent changes by X-rays as compared with their responsiveness to thermal agitation, or a break or loss must usually be produced by X-rays along with the gene change. The milder ultraviolet quanta, on the other hand, do produce gene mutations like the natural ones in these plants.

Such variations in effectiveness are, I believe, to have been expected. They do not shake our conclusion as to the accidental, quantum character of the event which usually initiates a gene mutation. But they give rise to the hope that, through further study of them, more may be learned concerning the nature of the mutation process, as well as of the genetic material that undergoes the changes.

Controlled Mutation?

No one can answer the question whether some special means may not be found whereby, through the application of molar influences, such as specific antibodies, individual genes could be changed to order. Certainly the search for such influences, and for increasing control of things on a microscopic and submicroscopic scale as well, must be carried further. But there is as yet no good evidence that anything of the sort has been done artificially, or that it occurs naturally. Even if possible, there could be no generalized method of control of gene composition without far greater knowledge than we now have of the intimate chemical structure and the mode of working of the most complicated and diverse substances that exist, namely, nucleoproteins, proteins in general, and enzymes. The works of Sumner, Northrup and Stanley, together with those of other protein chemists, point the way in this direction, but everyone will agree that it is a long and devious system of roads which is beginning here.

It is true that some cases are known of mutable genes which change selectively in response to special conditions. Such cases may be very informative in shedding light on gene structure, but we have as yet no indication that the alterations of these genes, which in the great majority of instances known are abnormal genes, have anything in common with ordinary natural mutations. It is also true that cases are known among bacteria and viruses of the induction of particular kinds of hereditary changes by application of particular substances, but here the substances applied are in each case the same as those whose presence is later found to have been induced, and so there is every reason to infer that they have in fact become implanted in some way, that is, that we do not really have a specifically induced mutation.

So far, then, we have no means, or prospect of means, of inducing given mutations at will in normal material; though the production of mutations in abundance at random may be regarded as a first step along such a path, if there is to be such a path. So long as we cannot direct mutations, then, selection is indispensable, and progressive change in the hereditary constitution of a living thing can be made only with the aid of a most thoroughgoing selection of the mutations that occur since, being non-adaptive except by accident, an overwhelming majority is always harmful. For a sensible advance, usually a considerable number of rare steps must be accumulated in this painful selective process. By far the most of these are individually small steps, but, as species and race crossings have shown, there may be a few large distinctive steps that have been, as Huxley terms it, "buffered", by small changes that readjust the organism to them. Not only is this accumulation of many rare, mainly tiny changes the chief means of artificial animal and plant improvement, but it is, even more,

the way in which natural evolution has occurred, under the guidance of natural selection. Thus the Darwinian theory becomes implemented, and freed from the accretions of directed variation and of Lamarckism that once encumbered it.

It is probable that, in a state of nature, most species have a not very much (though somewhat) lower frequency of gene mutation than would be most advantageous for them, in consideration of the degree of rigor of the natural selection that occurs in the given species. A much higher frequency would probably lead to faster genetic degenerative processes than the existing selection could well cope with. But, under conditions of artificial breeding, where selection can be made more effective, a higher mutation frequency can for a time at least be tolerated in some cases, and larger mutations also can be nursed through to the point where they become suitably buffered. Here it may become of practical use to apply X-rays, ultraviolet, or other means of inducing mutations, as Gustafsson especially has demonstrated for X-rays. This will be especially true in species which naturally undergo much inbreeding, or in which there is a well expressed haploid phase, or a considerable haploid portion of the genotype, for under these circumstances many of the spontaneous mutations that might otherwise have accumulated in the population and that could be brought to light by inbreeding, will have become eliminated before they could be found, and the natural mutation rate itself will be lower.

We have above largely confined ourselves to considering the relation of the production of gene mutations to the problems of the general method of evolution, including that of the nature of hereditary variation, because this has been, historically, the main line of approach to the subject of artificial mutations. It was from the first evident, however, that the production of mutations would, as we once stated, provide us with tools of the greatest nicety, wherewith to dissect piece by piece the physiological, embryological, and biochemical structure of the organism and to analyze its workings. Already with natural mutations, such works as those of Bonnevie, Grueneberg, Scott-Moncrief, Ephrussi and Beadle, etc., have shown how the intensive tracing of the effects, and interrelations of effects, of just one or a few mutations, can lead to a deeper understanding of the complex processes whereby the genes operate to produce the organism. But there are thousands of genes, and it is desirable to be able to choose them for study in an orderly fashion as we proceed with our dissection process. For this purpose we have thought that it would often be advantageous to produce mutations artificially in abundance, so as then to take our pick of those more suited for successive steps in our analysis. The work of Beadle and his co-workers on *Neurospora* in recent years, followed by similar work of Malin and Fries and of others, has brilliantly shown the applicability of this method for studies of the paths of biochemical synthesis of amino-acids, vitamins, purines and pyrimidines. And yet, in a sense, the surface of the subject as a whole has barely been scratched, and we may look forward with confidence to the combination of this technique with that of tracer substances and with all the other techniques of biochemistry, physiology and experimental embryology, for the increasing unravelling of that surpassingly intricate tangle of processes of which the living organism is constituted. There is no time, however, to go further into this subject here.

Chromosome Analysis

For we cannot neglect here a brief outline of another phase of the artificial mutation work, more specifically of interest to geneticists: that is, the further analysis of the properties of the chromosomes and their parts, gained chiefly from studies in which parts have been removed, added, or rearranged. We have already spoken, in passing, of the studies of the mechanism of such structural change, in which a relatively simple general scheme lying at the basis of all such alterations has emerged: namely, break-

age first, followed by adhesion of broken ends. It was early evident that by the use of such rearranged chromosomes additional proof of the physical validity of the linkage maps could be obtained, and this was done (Muller and Painter). Furthermore, it has been possible to throw light on problems of crossing over, as in the demonstration (Muller, Stone, and Offermann) that to whatever position the centromere is moved, it causes a strong inhibition of crossing over, the strenth of which gradually diminishes with distance. Moreover, the same proves to be true of any point of discontinuity in pairing, caused by heterozygosity in regard to a structural change. Such studies on crossing over, and on the pairing forces that affect segregation, are still capable of considerable extension.

We must remember, in speaking of the centromere and other apparently distinctive chromosome parts, that we have no right to infer that they are autonomous, locally determined structures, dependent on the genes of the regions in which they are seen to lie, before observations have been made that show the effects of removing or displacing those regions. Therefore, it has in the main been necessary to wait for the study of induced inversions, deletions and translocations of chromosomes, before the inference could be secure that the centromere is, in most instances, such an autonomous organelle, dependent upon a gene or genes in the immediate neighborhood (but not in all instances in the neighborhood, as Rhoades has recently shown in a special strain of maize). Similarly, it has been possible to show (despite some contrary claims, the validity or invalidity of which cannot be discussed here) that the free end of the chromosome, or telomere, constitutes in much material a locally determined distinctive structure.

By a combined genetic and cytological analysis of various cases of breakage and rearrangement of parts, it was found that there are distinctive, largely locally determined, regions of the chromosomes, usually most markedly developed near the centromeres, which we at first called "inactive" but which are now usually referred to as "heterochromatic." These were also found independently in purely cytological studies by Heitz. It would be fascinating to enter here into a discussion of the remarkable peculiarities which the cytogenetic studies have shown these regions to have—the evidence of repetition of more or less similar parts, of a tendency to conjugation between the differently placed parts, of distinctive cytological appearance correlated with whether or not such conjugation occurs, of inordinately high tendency to structural change, of strong influence of certain of their genes upon segregation, etc.,—and then to go on to discuss hypotheses of their evolutionary origin and their functions. This would unfortunately take us too far afield. We must, however, insist upon one point—as it is not yet generally enough recognized,—namely, that the evidence is very strong that what, in the *Drosophila* chromosome as seen at mitosis, is called "the heterochromatic region," is simply a large temporary body of accessory, non-genic nucleoprotein, produced under the influence of one or two particular genes from among the dozen or more that constitute the whole heterochromatic region, as detected by genetic analysis and by the chromosome as seen at the resting stage (as in the salivary gland). And it is not these conspicuous non-genic blocks which are responsible for the other known peculiarities of the heterochromatin, above mentioned—the function of the blocks is still undetermined. In other words, the so-called "heterochromatin" with which the cytologist deals in studying mitotic chromosomes is a quite different thing from, although in the neighborhood of, the heterochromatin proper having the above described complex of properties. Moreover, it has been possible to show (Sutton-Gersh in collaboration with the author, unpublished) that the conspicuous nucleoli often associated with the heterochromatin are produced under the influence of still other autonomous genes in it, that are separate from those for the mitotically visible blocks.

One of the most interesting findings which has come out of the study of *Drosophila* chromosomes that underwent rearrangement of parts as a result of irradiation has been the generalization of the existence of the phenomenon known as "position effect." This effect was first found by Sturtevant in the case of the spontaneous mutant known as Bar eye, but it was not known to what extent the effect might be a special one until numerous rearrangements could be studied. The term position effect implies that the functioning of a gene is to a certain extent at least dependent upon what other genes lie in its neighborhood. There is now adequate evidence that this is a general principle, applying to very many if not all the genes in *Drosophila,* and that their functioning can be qualitatively as well as quantitatively conditioned by the character of the genes in their vicinity, some of the genes having much more effect than others and different genes working in different ways and to different extents.

It is possible that, as Sturtevant suggested, the position effect is caused by the interaction between gene products in the vicinity of the genes producing them, assuming that such products are more concentrated there and under such circumstances tend to react more with one another than when dispersed. However, the interpretation which we favor is that the functioning of the gene is affected by its shape and that this, in turn, varies with the strength and nature of synaptic forces acting on the region of the chromosome in which it lies. These might consist of forces directly exerted on the gene by other genes, whether allelic or not (Muller), or they might be resultants of the state of spiralization, etc., of the chromosome region, circumstances which in their turn are in part dependent on synaptic forces (Ephrussi and Sutton). This interpretation, in either of its variants, would explain why position effects are so much more general in *Drosophila,* an organism in which the synaptic forces are known to operate strongly even in somatic cells, than in other organisms tested, in which such forces are much weaker or absent in somatic cells. It would also fit in with the author's findings that the heterochromatic regions tend to have especially strong, extensive, and distinctive kinds of position effects, effects varying in degree with the total amount of heterochromatin present in a cell, as well as with vacillating embryological factors. For these genetic findings are in conformity with the cytological effects of heterochromatin, observed first by Prokofyeva, on the degree of extension, synaptic properties, etc., of euchromatin in its neighborhood, effects which she showed to be subject to similar vacillations, that are correlated with the variations in the phenotypically observed position effects. Recent observations, both by Ephrussi and by Sutton, following suggestions of the author, and by Stern, also seem to point in this direction, for they show an influence, on the position effects exhibited by given parts, of the arrangement of *homologous* chromosome parts. If this interpretation based on gene shape should hold, it would open up a new angle of attack on the structure and method of functioning of the gene, perhaps ultimately relating it to nucleoprotein composition and properties.

Another use to which the process of breakage and rearrangement of chromosome parts by irradiation has been put is for the study of the effects of adding and of subtracting small pieces of chromosomes, in order to determine the relation of gene dosage to gene expression. In this way, it has been found out (1) that most normal genes are, even in single dose, near the upper limit of their effectiveness, and (2) that most mutant genes have a final effect qualitatively similar to but quantitatively less than that of their allelic normal gene. The dominance of normal genes over their mutant alleles, then, turns out in most instances to be a special case of the principle that one dose of a normal gene usually produces nearly though not quite as much effect as two doses. This in turn is best understood as resulting from a long course of selection of the normal

gene and its modifiers for stability of expression, when under the influence of environmental and genetic conditions which would affect the gene's operation quantitatively, *i.e.* in a manner similar to that of dosage changes. This does not mean that selection has specifically worked to produce dominance of the normal gene over its alleles, however, because (3) not all mutant genes behave merely like weaker normal genes, and (4) those which the dosage tests show to produce qualitatively different effects from the normal genes seem oftener to escape from the principle of being dominated over by the normals, just as would be expected on our hypothesis.

Among the further results of gene dosage studies carried out by the use of chromosome fragments produced by irradiation, attention should be especially called to the findings coming under the head of "dosage compensation." These have shown (1) that, when the dosage of virtually all genes in the *X* chromosome except a given one is held constant, the expression of that one is usually so very nearly the same when present in one dose as in two that no difference in the character can ordinarily be seen, and (2) that nevertheless this invisible difference has been so important for the organism that, in the course of the past natural selection, a system of modifying genes, called compensators, has been established, having the function of making the effects of the one and two doses normally present in the two respective sexes much more nearly equal still, when these dosage differences in the given genes are present simultaneously with those in all the other X-chromosomal genes. Each gene seems to have acquired a different system of compensators, the interrelations of all together being extremely complicated. This then gives evidence from a new angle of the meticulousness of natural selection, of the very precise adaptiveness of the characters existing in a species, and of the final grade of a character having ordinarily become established through the accumulation of numerous small mutations having very complex functional relations with one another. It is in line with our previous thesis of evolution through the selection of multitudinous tiny accidental changes.

When attention is concentrated on a given very circumscribed region of a chromosome, by a comparison of various induced rearrangements all of which have a point of breakage within that region, other facts come to light, bearing on the problems of chromosome and gene divisibility. By means of special genetic methods, which cannot be detailed here, evidence has been obtained that the breaks in any such limited region tend to occur at specific points, giving indication that discrete units or segments lie between these points, and thus arguing against the idea of the chromosome being a continuum and in favor of its genes corresponding to physical entities rather than merely to concepts arbitrarily set up for the convenience of geneticists. We are also enabled in this way to make estimates of the probable number of genes in the chromosome, as well as to get maximally limiting figures for their size. These estimates agree as closely as could have been expected with those based on previous genetic work, using entirely different methods, although not with the estimates based on the "sensitive volume" hypothesis.

Duplications and Evolution

Another finding made in studies of cases having a small fragment of chromosome moved, as a result of irradiation, to another position, was that individuals are frequently able to survive and reproduce even when they have the given chromosome part present in its original position as well as in the new position. In fact, it was in work of this kind that the effect of extra doses of genes was determined. Now, in some of these cases stocks could even be obtained which were homozygous for the duplicated piece as well as for the original piece. This led to the idea that duplications of chromosome material might in this manner have become established in the previous course of evolution. When, in the analysis of a limited region of the

X chromosome, including the locus of the so-called "scute" effect, it was found that there are in fact, within the normal *X* chromosome, two genes of closely related effect ("achaete" and "scute") very close or adjacent to one another, it became evident that this was in all probability an example of the above postulated occurrence. This then showed the way, and apparently the main if not the only way (aside from the far rarer phenomena of polyploidy and "tetrasomy"), by which the number of genes has become increased during the course of evolution. By a curious coincidence, Bridges was at the same time making his studies of salivary chromosomes and finding direct cytological evidence for the existence of such "repeats," as he called them, in the normal chromosome, and he interpreted these in the same manner. In the twelve years since that time, various other clear cases of the same kind have been demonstrated. Thus, increase in gene number, brought about by the duplication of small parts of chromosomes, more usually in positions near their original ones, must be set down as one of the major processes in evolution, in addition to the mutations in the individual genes. By itself, this process would not be of great importance, but it becomes important because, by allowing gene mutations to come afterwards that differentiate the genes in one position from the originally identical ones in the other position, the number of different kinds of genes is increased and so the germ plasm, and with it the processes of development and the organism as a whole, are eventually enabled to grow more complex.

Rearrangements of chromosome parts which do not lead to an increase in gene number can of course also occur in evolution, although it is unlikely that their role is so fundamental. By producing such changes in the laboratory it has been possible to find out a good deal more about what types can arise, and what their properties are. Various inferences can then be drawn concerning the viability and fertility that the different types would have, under varied genetic circumstances, and whether they would tend to become eliminated or to accumulate in a population of a given type. Some of them can be shown to have, under given conditions, an evolutionary survival value, both by aiding in the process of genetic isolation and in other ways, as by affecting heterosis. In this manner, evolutionary inferences have been drawn which have later been confirmed by comparison of the chromosome differences actually existing between related races, sub-species, and species.

Probably of greater ultimate interest will be the results of studies of gene mutations occurring at individual loci. Radiation mutations are frequent enough to lend themselves to comparisons of the potentialities of different loci, although not nearly enough has yet been done along these lines. Similarly, a comparison of the different mutations which can occur at the same locus can lead to very important results, especially since it has been shown that the different alleles may have every complex relationships to one another, so as even, in some cases, to reconstitute the normal type when they are crossed together. The way in which genes may change as a result of successive mutations remains to be gone into at much greater length. So, too, does the question of changes in gene mutability, brought about by gene mutation itself.

Somatic Radiation Effects

The further the analysis of the genetic effects of irradiation has gone, particularly of the breakage and rearrangement of chromosome parts, the more does our conviction grow that a large proportion if not the great majority of the somatic effects of irradiation that have been observed by medical men and by students of embryology, regeneration, and general biology, arise secondarily as consequences of genetic effects produced in the somatic cells. The usefulness of this interpretation has been shown in recent studies of Koller, dealing with improved methods of irradiation of mammalian carcinoma. This is too large a subject

to digress upon here, but it is to be noted that it has been the analyses based in the first place on genetic and cytogenetic studies of the reproductive cells, as shown by subsequent generations, which are thus helping to clear the way for an understanding of the mechanism by which radiation acts in inhibiting growth, in causing sterilization, in producing necrosis and burns, in causing recession of malignant tissue, and perhaps also, on occasion at least, in inducing the initiation of such tissue.

During the war years, a curious confirmation of the correctness of the above inference regarding the nature of the somatic effects of irradiation has come to light. While working with mustard gas in Edinburgh, J. H. Robson was struck with the remarkable similarity between the somatic effects of this agent and those produced by X-ray and radium irradiation. This led him to wonder whether perhaps mustard gas might produce genetic changes of essentially the same kind as those known to be brought about by irradiation. Comprehensive experiments were thereupon undertaken by C. Auerbach, working in collaboration with Robson, and (as mentioned on p. 263) she succeeded in showing that in fact this substance does produce mutations, both in the individual genes and by breakage and rearrangement of chromosome parts, such as X-rays and radium do, and in similar abundance. Other substances of the same general group were then found to have a similar effect. This constitutes the first decided break in the chemical attack on mutation. The fact that these findings were made as a direct result of the above inference, when so many previous attempts to produce mutations by chemical means had failed, appears to provide strong evidence that these peculiar somatic effects are in truth consequences of the more underlying ones which, when occurring in the germ cells, are analyzed by the geneticist in his breeding tests. There are, however, some very interesting differences between the nature of the genetic effects of irradiation and of these chemicals, which we cannot go into here, but which give promise of allowing an extension of the genetic and somatic analyses.

We see then that production of mutations by radiation is a method, capable of being turned in various directions, both for the analysis of the germ plasm itself, and of the organism which is in a sense an outgrowth of that germ plasm. It is to be hoped that it may also, in certain fields, prove of increasing practical use in plant and animal improvement, in the service of man. So far as direct practical application in man himself is concerned, however, we are as yet a long way from practicing any intentional selection over our own germ plasm, although like most species we are already encumbered by countless undesirable mutations, from which no individual is immune. In this situation we can, however, draw the practical lesson, from the fact of the great majority of mutations being undesirable, that their further random production in ourselves should so far as possible be rigorously avoided. As we can infer with certainty from experiments on lower organisms that all high-energy radiation must produce such mutations in man, it becomes an obligation for radiologists — though one far too little observed as yet in most countries—to insist that the simple precautions are taken which are necessary for shielding the gonads, whenever people are exposed to such radiation, either in industry or in medical practice. And, with the coming increasing use of atomic energy, even for peacetime purposes, the problem will become very important of insuring that the human germ plasm—the all-important material of which we are the temporary custodians—is effectively protected from this additional and potent source of permanent contamination.

COAT COLOR, PHYSIQUE, AND TEMPERAMENT

Materials for the Synthesis of Hereditary Behavior Trends in the Lower Mammals and Man

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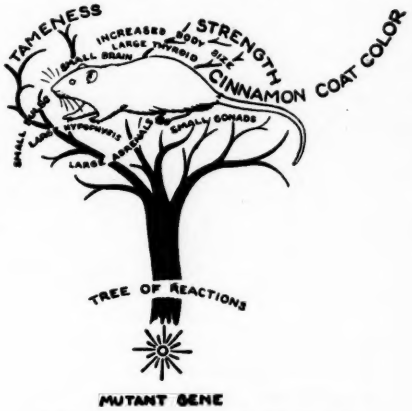
IN a number of contributions the author and his associates have shown that certain genes markedly affecting coat color additionally manifest themselves in all parts of the mammalian organism by producing modifications of morphology. Furthermore these coat-color mutations in some instances modify physiological natures, and condition the expression of unique trends in behavior.

Elsewhere we have represented diagramatically the effects of a single gene upon various developmental reactions by means of the branching of a tree of consecutive chains of reaction. The tips of the twigs symbolize the completion of physical development, that is, the fully developed organs with which the Norway rat, for example, carries on the business of life.

The hypothesized mechanism of relationship between a mutant coat color gene and its correlated modifications of morphology, physiology and behavior is illustrated for the male cinnamon rat in Figure 1.

The ontogenetic mechanism which translates gene-potentials into adult form-and-function is much more complicated than this because we know that all physical characteristics are affected by numerous genes. Many of these genes (possibly most of them) interact with each other. We may improve our picture by saying that total development is somewhat like a dense jungle of interwoven trees of reaction, extending from many genes at the ground level to the topmost jungle of branches and twigs in the completed organs. If we imagine the trunk and branches of one tree in this jungle of reactions to be changed to bright yellow (or some other contrasted color) rather than the usual drab brown, we get a better idea of the reactions that are changed by the mutant gene, because the mutant gene expresses itself, naturally, only in the presence of all the other genes essential to the development of the organism.



PSYCHOSOMATIC PLEIOTROPY

Figure 1

This "tree of reactions" shows the modifications found to be correlated with the presence of the cinnamon gene in the Norway rat. The total developmental mechanism would be represented by a dense jungle of many such "trees," intricately interlaced.

According to this view, the mutated or altered gene initiates a complex series of altered biochemical reactions, these reactions setting off still other altered reactions, and so on.

An altered hereditary factor or gene produces its altered developmental reactions throughout the whole body of the animal, altering slightly such things as body size, relative proportions of bodily parts, glands, sense organs, brain and hair color. Some of these struc-

tural changes, in turn, modify physiology and the modified physiology produces altered behavior trends some of which are measurable.

If one removes the mutant hair color genetically, (i.e., by substituting some allele), one automatically lifts out the whole tree of associated reactions and effects, including the mutant gene that caused them.

Granting that the above is a reasonably accurate description of the process, if the experimenter, by means of the coat-color handle, lifts out several trees of altered gene reactions, he may combine them together by means of genetic techniques in order to synthesize new, combinational trends in morphology, physiology, and behavior.

In the coat-character-behavior correlations we have a method of determining, directing, or biasing the behavior of individuals in response to their environment. Because the physical basis for such biases is simply inherited it may be compounded by adding together different mutant coat-character genes, which gene complexes may be made by selection to characterize, in turn, whole strains of animals. This mechanism gives into our hands the power to direct the evolution of the behavior of mammalian species, even including man.

I have shown that it is possible to synthesize extremely different behavior patterns in rats by combining two or three mutant coat-character genes, each having small specific effects on morphology, physiology, and behavior.

If the situation represents a general principle, then the Norway rats that we have described previously should not constitute a unique situation. Individuals bearing various mutant coat-character genes among numerous species of mammals should exhibit correlated alterations in morphology, physiology, and behavior.

I announced in 1941 the discovery of a number of morphological, physiological, and behavioristic trends associated with coat character genes in rats, and in 1942 I reported statistical proof of the taming effect of the black non-agouti gene. As was to be expected some prominent biologists were openly skeptical as to the existence of such correlations. One who commended the work said, "I scarcely dare to believe it."

Recently a noted mammalogist suggested that "perhaps these reputations are in the category of old wives tales." Even one observer, who believed that he saw tameness associated with a coat color, added, "I cannot be sure that one of us did not sell the other the ideas."

Such a stage of general skepticism and justifiable doubt is exactly what was to be expected. Here fruitful lines of scientific investigation often start, and our first duty is to collect and eventually to sift all available isolated reports in order to select the materials most suited for further adequately controlled inquiry. To this end for the past five years I have sought to obtain from unimpeachable sources instances of correlation between coat-characters and morphology, physiology, and behavior. I have been impressed with the fact that it is not the imaginative person who is intrigued by the idea, but rather the careful, keen observer, who can describe particular cases. The more superficial person usually dismisses the question with "Never heard of such a thing!" Much of the following list of cases must of necessity be anecdotal, and unless otherwise stated, each story is contained in a personal communication to the author.

Albinos in General

Mr. E. P. Walker, assistant director of the Washington Zoological Park, says, "Albinos are almost invariably such weaklings that I feel sorry to see them exhibited. I have not checked upon the size of albinos but I know that some that I have observed were smaller than the average for their species and I have no doubt that this is generally true."

Horses

The Palamino, buckskin or California golden horse, is noted for its gentle and tractable disposition. A reiteration of this statement has appeared from time to time in farm and country magazines recently. Pedro Martinez, the Tucson cowboy, and other horse trainers agree with this statement.

Martinez tells the story of being in on a project to break a herd of some sixty wild horses. He singled out and lassoed one of the two dappled grays on the ranch. In three days

he was riding this animal to lasso other members of the herd. The other dappled gray had been tamed before his arrival and was being ridden by the ranch owner's young son because of its extreme trustworthiness.

This story fits well with the statement of Major Saunders, as quoted by Robert Cook.[7] "The great popularity of gray horses is apparently well-justified, but I am inclined to wonder if it is the color which made the reputation. Is it not possible that the coat is but the trade mark of a line which transmits good sense and steady conformation?"

Emerson Metoxen, chief of the Turtle Clan, Wisconsin Oneida Indians, tells me that as a boy, he and his comrades used to approach the herd of semi-wild Indian ponies that ranged their reservation, an apple in one hand and a noose of rope in the other. He said that it was most likely to be a palamino, a pinto, or an albino that was bold enough to come forward to get the apple and pay for it with a bareback ride. But should a bay, a dun or a sorrel be caught, the chances were great that the boy would not ride long.

A chief of the Omaha tribe of Indians, reports for the semi-wild Omaha herd of Indian ponies a complete confirmation of Chief Metoxen's account.

E. A. Daubenspeck of Shelby, Montana, reports: "We find that the average run of buckskins, albinos, and poorly bred palaminos are freaks in the literal sense and are generally classed as knotheads in this country."

Members of the Bridle Club of Greensboro, N. C., tell of the stamina of bays, sorrels, and duns in a race, but emphasize the readiness with which blacks loose their "heart" or will to win in a contest of speed. I have heard this elsewhere.

Mrs. Valla Oehme, horse raiser and trainer, tells me that in her many years of experience with horses she finds Palaminos to be very tame and tractable. She finds that dappled grays in general are tame, but that chestnut horses tend to be unruly.

Prof. J. C. Bonner who has "ridden literally hundreds of cavalry horses" tells me that in his experience chestnuts are of unruly temperament, and that the blacks he has handled outside of the service tended to be slow and docile.

Mr. W. S. Kinney, horse trainer and dealer, says that buckskins caught on the range are slow and that dappled gray horses caught on the range are gentle and easy both to break and handle.

Some fifteen years ago a history of the west described how settlers used to single out and catch canyon horses bearing yellow fetlocks, because they could be tamed more readily than the others.

Darwin stated that Paraguayan horses, presumably with curly coat, had "mule feet," meaning, I suppose, feet of abnormally small relative size. I have seen a report stating that these animals are smaller than straight haired horses.

Cattle

An Oklahoma rancher relates how he bought a herd of sixty head of pedigreed Durham cattle in Virginia. Forty-five were brindled, but fifteen were black sports that had cropped out, their appearance being the reason why their wealthy breeder disposed of them. After a year on the range, the newcomer and his associates rounded them up to brand the calves, only to find that the brindled individuals had become so wild that they would attack a man on a horse. Such ferocity he had never observed in cattle before. But the black sports had remained so tame that one could dismount and pat them on the face like dairy cattle. A black cow would charge only when her calf was lassoed and thrown for branding.

Prof. M. B. Rodriguez reports that the small, black Spanish cattle of the Mexican bull fights are very tame until they are "trained" for the arena.

Prof. Wm. A. Richards says that if not confined, black Aberdeen Angus cattle in North Carolina are very tame as compared with brindled Durham cattle.

Probably related to Prof. Richards' account is that of the Argentine Ministry of Agriculture which reports that in comparison with Shorthorn and Hereford Cattle, the temperament of Aberdeen Angus is more active and they possess a greater irritability, facts which are accentuated when they graze in the fields and mountains. Whether this has anything to do with coat color is not known.

Dr. Joequin A. Cortez G., chief of the Department for the Promotion of Livestock Production (Fomento de la Produccion Pecuaria) of the Peruvian Government writes:

"The greatest power of reflecting back heat rays is possessed by the basic color red, which, above all, transforms into terminal energy the radiations of light of the color spectrum. On the basis of this fact the undersigned proceeds to interpret shortly—technically—a practical observation carried out in the year 1936, in the Departamento de Piura, during which a powerful illumination resulted in a temperature above normal, which was accompanied by a prolonged drought. These factors brought about an extraordinary mortality of cattle possessed by many ranches in this province. Without doubt, in certain localities, it was possible to observe that all the animals that were able to survive the action of these unusual phenomena, primarily excessive light and heat, possessed the basic color red."

My great-grandfather, Samuel Rowley, a western Pennsylvania colonist, told my father that he would never have a white or a black ox because their skin was thin and for this reason they would gall readily on the shoulders under the yoke. He preferred brindle, red, or Jersey colored oxen, that had thick skins.

Mr. J. W. Higgins, who helped his father in his business of clearing the virgin woodland of northwest Ohio, said that his father only saved for oxen calves of much the same colors as Samuel Rowley chose, but he never inquired why the selection was made.

Prof. J. C. Bonner, who as a boy snaked logs with an ox team in south Georgia, corroborates this observation so far as his oxen were concerned. He had a red and a black yolked together. The black was thin skinned and was always becoming galled.

The research laboratory of Armour and Company, Chicago meat packers, was approached as to the thinness of skin in black and piebald cattle. Their chief skinner replied that blacks and piebalds have thin skins compared with cattle of other hair colors.

An agricultural report from the Union of South Africa noted that the white areas of piebald cattle broke out in a rash when they ate certain plants. The same was reported for piebald guinea pigs.

O'Flaherty and Roddy[32] reported that when cattle hairs are treated with lime-sodium sulfide solution, crenation and then destruction occurs first in red hair, next in black hair and lastly in white hair both in samples from living animals and from green salted hides.

Darwin states that white cattle are more injured by flies than other colors are.

Sheep

The sensitivity of piebald cattle to certain herbs recalls the work of Heutzinger, referred to by Darwin, that told of white sheep being injured by the eating of certain herbs, whereas the colored animals showed no ill effects.

Swine

In the *Origin of Species* Darwin quotes Heutzinger's finding that white pigs as well as the white sheep mentioned above are injured by the eating of certain plants, whereas the dark-colored individuals escape.

This story fits well with the account that Prof. Jeffries Wyman wrote to Darwin, to the effect that in Florida pigs ate the paintroot (*Lachnanthes*) which colored their bones pink and which caused the hooves of all but the black varieties to drop off. In this fashion, it came about that the pigs of the Florida squatters were black.

In *Plants and Animals under Domestication*, Darwin refers to the better survival of black pigs in Virginia, and that white pigs are more readily affected by the sun.

Otto Mohr quotes the work of Ossent showing that the wild agouti coated swine are relatively immune to *Bacillus suisepticus*, whereas other colors are killed by the disease.

Dogs

A life-long trainer of dogs, Mr. H. R. Watson, says that in his experience, red cocker spaniels are more nervous and noisy than blacks.

I would concur with Mr. Watson's observations and add that I have collected some data to show that reds are more likely to be thin boned and lighter bodied than blacks.

Various fanciers have pointed out to me that black cockers are more likely to have a thick coat and more perfect feathering than are reds born in the same litter. One fancier says this difference in thickness of the coat is the reason for the popularity of red cockers in Georgia, since they are more likely to survive the summer heat.

I have noted the great difference in hair growth impetus between white areas and black spots especially on the sides and hind legs of piebald Spaniels. The white areas will often grow thin, short hair whereas the black spots will develop thick, long hair.

Dr. A. J. Lee, of England, tells me of the "weedy" constitution of chocolate colored Irish terriers.

Darwin says that white terriers suffer from distemper.

It is well known that white bull terriers with blue eyes are likely to be deaf. If the one eye is brown and the other blue, the animal may be deaf only on the blue-eyed side. The inner ear of the deaf side will be found to consist of an unorganized mass of black pigment.

Dr. Taku Komai tells me that "Breeders of the Japanese native dogs state that white dogs are decidedly more tame and often with a defective sense (e.g. deaf or imbecile)—as a matter of fact in old Japan, the white dogs are sometimes thought to be a reincarnation of a human being!, whereas the black or brown ones are more agile and courageous."

Dr. J. M. Phillips reports on cockers "Dilute livers and blacks have very brittle hair so that they look like mangy specimens with bare patches of skin visible by the time they are six months old, while dilute reds may have fair coats.

Blue Merle Collies are smaller than normal."

Foxes

Mr. E. P. Walker believes that in the early days of the silver fox industry, the silver strains then known tended to be wilder than the reds from which they were derived.

Mr. W. Whittingham, who has tried out all the known strains of Silvers, says that one strain will not offer to bite when picked up.

Prof. Joseph Peary says that a strain of Platinum foxes is very tame.

Cats

A case completely analogous to that of deafness of blue-eyed white bull terriers is found in white cats.

C. H. Danforth writes: "I am inclined to think that we have had more wild cats which were agouti, although some of the tamest ones have been agouti. We have had some very wild ones which carried the gene for dilution." However, it must be pointed out that these animals are random specimens and not many of them closely related.

Various zoo keepers, and professional trappers, attest to the greater savageness of the black leopard.

Mr. E. P. Walker says, "I am inclined to believe that black jaguars and black leopards are perhaps slightly less tractable than the normally colored ones."

Squirrels

Mr. Walker writes, "It appears to me that black squirrels are generally dominant in a group."

Clark and Jellison described[6] the tame behavior of pale ground squirrels (*Clitellus elegans*). Fichter and Davis[12] review this work as follows: "They observed these pale squirrels, which they considered as mutants, as being more tractable than the normal colored specimens immediately after capture, and quite docile after a short confinement." They continue, "It is of interest to note that the pale specimen of *Clitellus elegans tridecemlineatus* (of Fichter and Davis) has been at all times tractable, readily submitting to handling whereas her two sisters have exhibited unpredictable dispositions, even being aggressively pugnacious."

A letter from Fichter states: "'Blondie,' as the pale ground squirrel has been affectionately known for 3 years, was at all times tractable. She was not without temperament, however, often asserting herself with growling, threatening gestures with the front feet, and when being handled, with shoving motions of the muzzle against one's hand or fingers. She never attempted to bite. Her normal colored sister, while offered the same treatment, would never submit to handling. Blondie would climb the side of her cage upon one's approach, expecting to be handed some morsel of food."

Raccoon

I visited a color phase raccoon farm near Bucyrus, Ohio, a number of years ago and observed the notably poorer quality of stiff albino fur. Blacks appeared to have thinner fur than the grays, cinnamons and pink-eyed buffs. A questionnaire was sent to a list of Pennsylvania raccoon breeders in 1942 asking if they had noted any difference in behavior between grays and blacks. A few noted no difference, but the majority said that blacks were tamer than grays (nobody thought the opposite), that they were easier to tame than the grays, and that when once tamed and allowed their freedom about the farm house yard the blacks less frequently than grays returned to the woods.

Mink

A letter in 1942 to Charles Whitaker, an originator of platinum mink, brought the answer that from the beginning they were tamer than the normal colored mink from which they were derived.

Mr. Larry Moore writes, "In regard to the tameness of our mutation mink, I feel that the recessive mutations are tamer than our normal mink. However, I feel that the dominant mutations are of about the same nervous tendency as our dark mink. The blond or Royal Pastel mink are probably the most gentle of them all. We feel that when you cross the dominant and recessive and get what we call the Breath of Spring Silverblu, from breeding a Silverblu to a Blufrost second generation, that this animal is not as tame as the Silverblu recessive, but is possibly a little more gentle than the Blufrost dominant."

In 1946, Mr. Whitaker confirmed the observations of Mr. Moore on all mutant mink varieties.

Mr. W. Whittingham, originator of one strain of Platinum mink by mutation, has this to say: "The Platinum mink is tamer than the dark. We have two that we can carry and we have never had a dark mink that way. The females are the same. They do not exercise like the darks, so get fat and do not produce unless they are cut on feed. Our albinos are like the Plats, maybe not as gentle but not like the darks. And the Pastels are not as wild as the darks. The three strains or mutations are all recessive: Plats, Albinos and Pastels. The dominant Black Cross and Bluefrost are like the darks."

On the contrary, B. C. Backus, of Ward's Natural Science Establishment, tells me that in contrast with eastern mink, normal black Yukon mink tend to fatten and become sluggish unless their diet is watched carefully. He blames the docility of Platinums on Yukon ancestry and the viciousness of Blackcross mutants on excitable eastern ancestry. Thus, it will require a carefully conducted genetic experiment in order to determine whether or not these temperament differences observed in mutant mink are due to coat-color genes or to genes in the residual hereditary backgrounds of the animals, or to both. Mr. Backus' belief is not confirmed by the experience of Mr. Whittingham.

Peromyscus

Frank Clark reported the tame tendencies on the part of pink-eyed dilute *Peromyscus.*

Elizabeth Barto believes that ivory and silver *Peromyscus* on the whole are tamer and more lethargic than those with the wild-type coat color. Her recollection of the first pink-eye dilute mutation is that it was very docile.

R. R. Heustis says that he concurs in Miss Barto's estimates.

Rabbits

W. E. Castle has pointed out that greater size is associated with the chocolate gene in rabbits. It seems probable that size correlations will be found associated with other coat color genes.

More than twenty years ago, when I was a student assistant helping Dr. Castle weigh rabbits, certain individuals of the Vienna White strain used to suffer from epileptic fits, being stimulated apparently by the up and down mo-

tion of the scales. Today I have indications which suggest that the epilepsy be a manifestation of the Vienna White gene, occurring in about 10 per cent of segregating white individuals having one or both eyes blue.

Rats

Castle noted the greater size tendency associated with the chocolate (cinnamon) and the size-reducing tendency of blue gene in the Norway rat, *Rattus norvegicus*.

I have pointed out that in rats a tendency to weight-increase is associated with the cinnamon gene in both males and females and that a similar effect is associated with the curly gene in males, possibly also in females. Weight-decreasing effects were found in both male and female hooded rats, both male and female albinos, as well as in ruby eyed dilutes (both males and females). The interactions of these size tendencies have been described. Similar correlations were found for body length.

Other changes associated with coat-character genes in rats involved tail, testes, thyroid, pituitary, adrenals, femora, olfactory bulbs and nasal bones, brain weight, rate of natural water loss in bones and brain, possibly size and shape of foramen magnum, general activity, basal metabolism, heart rate, voice components, propensity for chewing wood, choice of diet and muscle tonus.

Farris and Yeakel[10] have confirmed the taming effect of the black (non-agouti) gene.

Dr. Komai informs me, "Those who have made a large collection of house rats [in Japan] unanimously assure that the piebald mutants, of which there are a few among thousands, are invariably more docile than the wild types. It is not clear, however, whether they are descendants of a white rat or entire new mutants."

Mice

Castle says of pink-eye, "Certain pink-eyed individuals have been noted in my records as 'jumpers,' because they refuse to remain quiet on the weighing scales long enough for one to observe their weight. Frequently they would turn back-somersaults and then scurry away to a corner of the room. I have never observed comparable behavior among dark-eyed litter mates of such pink-eyed jumpers."

I have noticed this nervous reaction in pink-eye mice, as well as "head weaving." These behavior traits are so marked that they must have been noticed by many other workers.

Feldman,[11] Green,[15,16] Castle *et alii*,[4] have all in turn noted the association of greater size with the chocolate (cinnamon) gene in mice. Castle *et alii* noted the growth promoter tendency associated with the short ear and pink-eye, genes.

Danforth reported the tendency to fatness in lethal yellow mice and Castle showed that their bone structure is increased in size.

I tested several litters segregating for normal and wavy hair form. The wavy animals were of smaller size.

In other experiments, I found an association between a principal silver gene and also the lethal yellow gene with the laying on of fat. One should mention the association of the dominant white gene with lethal anemia and a belly spot with infantile anemia.

Paula Hertwig discovered an association between a crippled leg condition and a hair dilution that she induced with x-rays.

Doubtless a large number of other correlations are known to persons handling inbred strains of mice segregating for coat colors.

Man

Fölling showed me in Oslo some of the phenylpyruvic idiot patients from whom he had described the disease. The associated blond hair may be in part due to the action of the sunlight, and so may not be considered as a natural end stage in pigment development. On one idiot of the Oslo group I noticed that the hair was dark for about a millimeter at the scalp end.

Various reports record the abnormally high rate of tuberculosis in Venetian blonds.[2] I have found confirmation of this in a sample of college students. Venetian blonds do not tend to freckle as do blue-eyed reds.

Many persons believe that red headed persons are more highstrung than the average, but so far as I am aware, convincing evidence has not been presented to date. One member of a family having numerous red headed members says that the reds have little resistance to disease, especially pneumonia.

Flesh and Rothman have reported the finding of a special iron compound in human red hair which they have named trichosiderin. This work suggests a new pigmentation series of reactions aside from the brown-black series.

Dr. Virginia Apgar, Director of Anaesthesia at the Presbyterian Hospital in New York City, says of red heads:

"Due to their thinner skin or to the diminished pigmentation of the skin, these patients show color changes much more vividly than usual. For example, in the head down position or after an ample dose of scopalamine, their skin appears to be bright red while on the other hand, any degree of oxygen lack will make their skin appear remarkably cyanotic; it is possible that a more ample supply of skin capillaries contributes to this observation, a fact supported by the observation that there is more bleeding from the skin when an incision is made. It is also our impression that these patients exhibit vasometer instability to a marked degree for which we have no explanation."

Dr. Paul M. Wood, Secretary-Treasurer of the American Board of Anaesthesiology, writes, ". . . in twenty-two years of personal experience I have discovered that many difficulties have occurred with persons who have red hair. They do not seem to take anaes-

thetics in the same way that others do. Most of them are much more sensitive to the anaesthetic."

Dr. David M. Levy states that red headed persons in general go under anaesthetic more readily than do persons of other pigmentations.

Dr. Marco Nunez confirms these observations that red heads are affected more readily than are other persons.

There are reports in the medical literature to the effect that blonds are less efficient in their use of vitamin A than are brunettes.

J. Grieve finds in man that "there seems to be a small but definite relationship between defective color-vision and dark pigmentation of the iris."

Cyril Burt says, "increased frequency of color-deficiency among dark-eyed groups is fully significant."

Conclusion

There are already enough cases of correlation known between hair characters and morphological, physiological and behavioristic trends, to make worth while the singling out, for detailed study, of specific trees of interrelated morphological, physiological and behavioristic phenomena in the lower mammals and man.

These studies should lead to the synthesis of complex behavior trends in both mammals and man by the employment of the coat-character handle technique described above.

It is hoped that this account will stimulate others to place on record additional coat-character behavior observations and to undertake the synthesis and study of genetic behavior trends.

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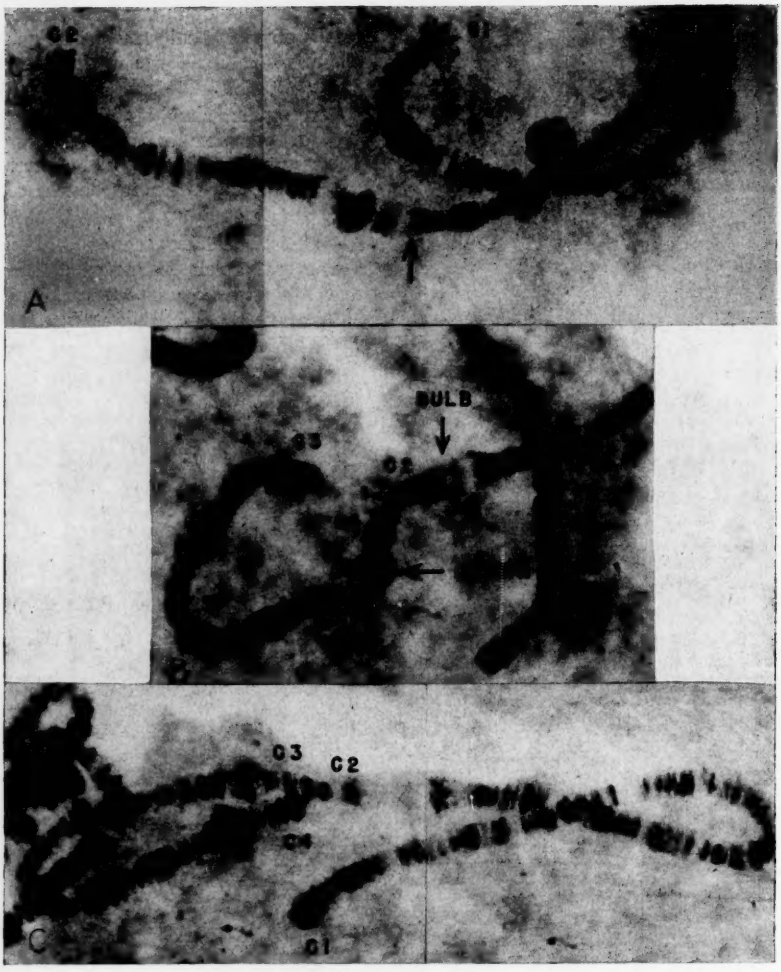

CHROMOSOMES OF TWO SCIARA SPECIES

Figure 2

A—The normal chromosome *C* as observed in the salivary gland nuclei of unisexual and bisexual strains of *S. ocellaris*. The arrow indicates the point of break in the natural terminal inversion shown in Figure 7*B*. *B*—A portion of banded chromosome *C* of *S. reynoldsi*. Ends *C2* and *C4* are partially stuck together. End *C1* is not shown in this figure. Two characteristic landmarks referred to in the literature as the "bulb" and the "crown" are indicated near *C2* and *C4* respectively. *C*—The normal banded *C*-chromosome of *S. reynoldsi* showing the characteristic morphology of all four "ends." *C2, C3,* and *C4* are stuck together.

CHROMOSOME EVOLUTION IN SCIARA

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CHROMOSOME changes, either at a microscopic (i.e., cytological) or submicroscopic (genetic) level, have come to be recognized during the past twenty years as the main source of permanent, hereditary variations. Comparative genetic and cytological studies on the same or closely related species have given students of evolution important insights into the kinds of chromosomal alterations which have accompanied speciation. Outstanding in this field has been the work of Sturtevant, Dobzhansky, and others on *Drosophila*. This genus is particularly favorable for such investigations because of its giant salivary gland chromosomes, an advantage shared with other Diptera. In these groups, therefore, where the chromosomes can be examined in minute detail, comparative studies of chromosome geography are of great importance. Several studies of this nature have been undertaken on *Sciara* in Dr. Metz's laboratory. The main objective of this work has been to determine whether the principal types of natural chromosome alteration found in *Drosophila* are likewise characteristic of *Sciara*. The initial study, undertaken by Metz and Lawrence[6] on species hybrids between *S. ocellaris* Comstock and *S. reynoldsi* Metz, seemed to indicate an apparently fundamental difference between the two genera. Whereas in *Drosophila* the principal changes involve gross rearrangements, especially inversions, and few minute modifications of the duplication-deficiency variety, the reverse seemed to be the case in the *Sciara* hybrid. There was a rarity or possible absence of inversions and translocations, and the natural chromosome variability in *S. ocellaris* was found to be represented entirely by small differences in banding[5].

Subsequent studies have revealed, however, that as regards gross rearrangements the conditions in *Sciara* are not so distinctly different from those in *Drosophila*. Carson[1], in a very intensive study on wild populations of *S. impatiens*, found twelve inversions and thirteen small differences of the duplication-deficiency type distributed among the four chromosomes. And McCarthy[4], in a less detailed examination of eight other species of *Sciara*, found inversions in five and minute differences in banding in six of them.

Recently Rohm[7] presented a paper on the evolution of chromosome *C* in the interspecific *ocellaris-reynoldsi* hybrid originally studied by Metz and Lawrence[6]. It is to be recalled that the latter authors found no evidence of gross rearrangements in the chromosomes of the hybrid. They recognized in chromosome *C* of *reynoldsi*, however, a peculiarity which did not exist in the *ocellaris* homologue; namely, the regular transverse separation of chromosome *C* in the salivary gland nuclei into two approximately equal segments during the course of larval development (See Figure 2*B*, 2*C*, 3, 4 and 5*A*). Such a separation does not occur in salivary gland chromosome *C* of *ocellaris* (Figure 2*A*); nor does it occur in the germ line chromosome of either species. Rohm[7] undertook a refined analysis of chromosome *C* in various strains of *ocellaris* and *reynoldsi* and in the interspecific hybrid. On the basis of the homologies worked out, she has suggested two alternative evolutionary schemes for the derivation of the *reynoldsi C* from the *ocellaris* standard; one involves a single transposition of

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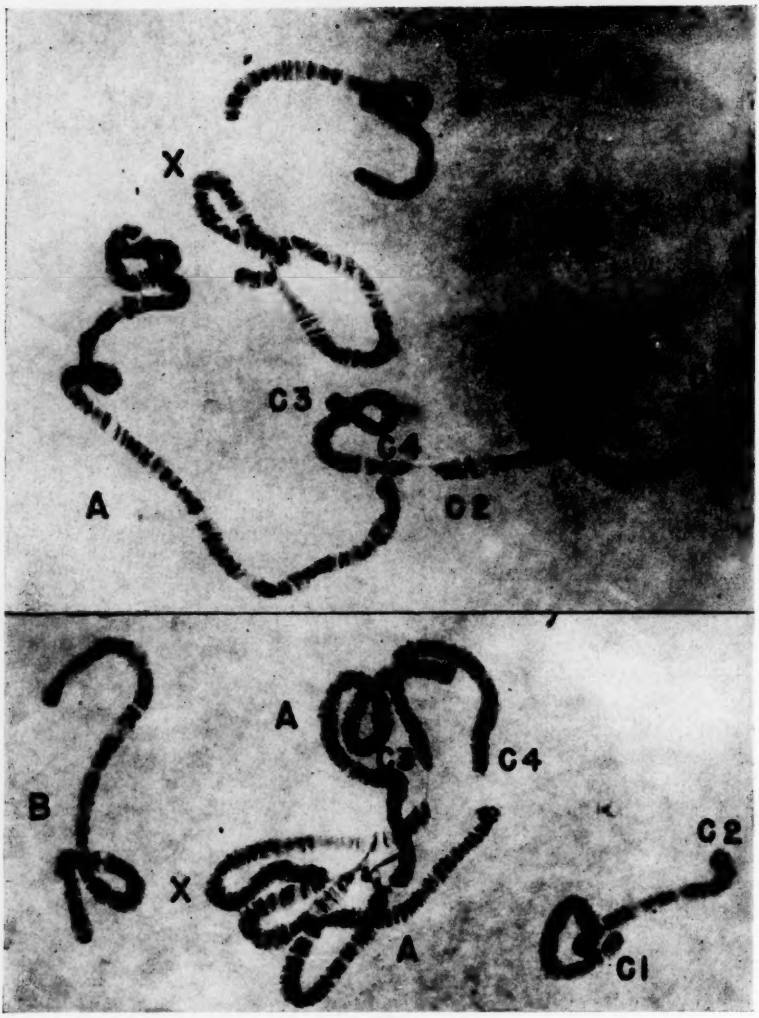


DETAILS OF *C* CHROMOSOME OF REYNOLDSI

Figure 3—Upper Photograph

The complete chromosome complement as observed in the salivary gland nuclei of *S. reynoldsi.* All four "ends" of *C* are designated. The two segments of *C* are only partially separated, *C2* and *C4* being stuck together.

Figure 4—Lower Photograph

Same as Figure 3, except that separation between two segments of *C* is complete and consequently *C1, C2, C3,* and *C4* lie free in the nucleus. It is very unusual in this material to find preparations in which all of the chromosome ends are free.

chromosomal material, the other a series of two included inversions.

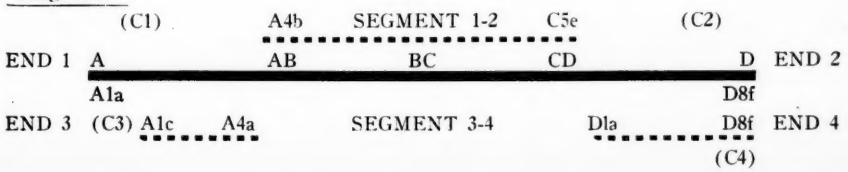
In studies on induced and natural chromosome rearrangements the writer has secured new evidence which shows that a somewhat different interpretation of this case is necessary. As brought out in the following account, it seems probable that the evolutionary changes have been more complicated than those postulated by Rohm and that a process of terminal inversion has been involved.

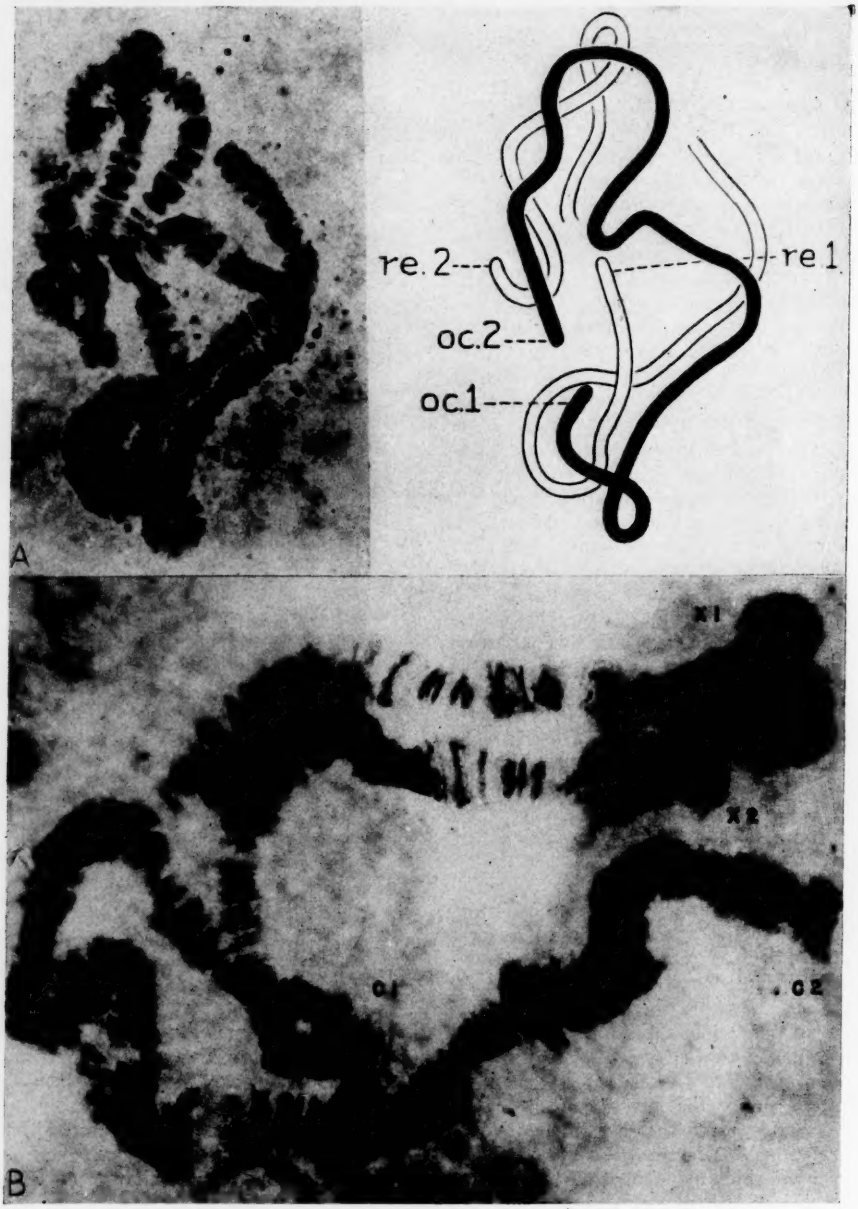
The basic haploid set of chromosomes in both *ocellaris* and *reynoldsi* is four. At metaphase this set in *reynoldsi* consists of two rods and two V-shaped chromosomes.[2] The smaller V has been identified[3] as chromosome *C*. In *ocellaris*, on the other hand, the homologous chromosome *C* may be either V- or rod-shaped at metaphase. Despite the shift in position of the centromere, the two chromosomes pair neatly in the salivary gland nuclei with no evidence of inversion or any other gross rearrangement of material.[2] It should be noted also that individuals of *ocellaris* homozygous for the V-shaped chromosome do not show the transverse separation of *C* into two segments in the salivary glands (Figure 2*A*) as is characteristic of *reynoldsi* (Figures 2*C*, 3, and 4).

In her comparative study on chromosome *C*, Rohm considered the *ocellaris* condition to be 'standard' and *reynoldsi* to be derived. To the *ocellaris* standard she assigned five major map units, *AA* to *DD*, and to the two approximately equal segments of the *reynoldsi* chromosome she allotted a corresponding number of units. On the basis of synaptic attraction in the interspecific hybrid she was able to determine the homologous relationships in the two species. These relationships are shown diagrammatically below.* Rohm's terminology is used throughout. The *ocellaris* chromosome is represented by the solid line and the two segments of the *reynoldsi* homologue by the broken line above and below the solid one. The map of the *ocellaris* chromosome is divided into four large sections. Beginning at End 1 they are lettered A—A, B—B, C—C, and D—D. Each of the sections Rohm has subdivided into smaller regions 1, 2, 3, etc., and assigned letters *a*, *b*, *c*, etc., to the individual cross bands. Segments 1-2 and 3-4 of the *reynoldsi* chromosome are represented respectively above and below the *ocellaris* standard by the broken line. It is convenient to have the chromosomes so arranged that homologous regions lie opposite each other. Segment 1-2 of *reynoldsi* is homologous to one continuous section of the *ocellaris* chromosome, extending from A4b to C5e. Segment 3-4 is arbitrarily represented in two parts, one at the lower left and one at the lower right, both parts lying opposite the corresponding *ocellaris* regions. Actually, of course, these parts are not separate but form a continuous segment of chromosome, including A1c to A4a and D1a to D8f; D1a follows immediately upon A4a. (See Diagram 1.)

As a result of the tranverse separation into two segments, the *reynoldsi* chromosome has four ends, designated respectively C1, C2, C3, and C4. Sometimes all four ends lie completely free in the nucleus as in Figure 4. Usually, however, they are partially stuck together. For example, in Figures 2*B* and 3, C4 is stuck to C2; and in Figure 2*C*, C2, C3, and C4 are all three in contact. This phenomenon of stickiness is by no means restricted to chromosome *C* of *reynoldsi*. All of the salivary gland chromosomes in this species characteristically display a stickiness of the end re-

***Diagram 1.**





HYBRID AND TRANSLOCATED CHROMOSOMES

Figure 5

A—Chromosome *C* as observed in the salivary gland nuclei of the interspecific hybrid of *Sciara ocellaris and S. reynoldsi.* This figure is taken from Metz.[6] Metz did not use the *"C1, C2, C3, C4"* terminology adopted later by Rohm; "re 1" and "re 2" in the outline drawing correspond to *C2* and *C4* respectively. *B*—An x-ray induced translocation between chromosomes *X* and *C* of *S. ocellaris.* The point of translocation is very near end *C1*; consequently, the translocation chromosome *C1-X2* is quite short while the other translocation chromosome, *C2-X1,* is very long. Mitotic chromosomes *X* and *C* both have a subterminal centromere, and that on *X* is known to be located near end *X1* in the salivary gland nuclei. The centromere of *C,* therefore, has to be located within the short *C1* arm of this translocation cross (see text).

gions; and apparently the terminal adhesions that are formed among the different chromosomes occur at random. Cells such as those shown in Figures 3 and 4, in which there is only one terminal adhesion, are obtained very rarely. Ordinarily about three-fourths of the chromosome ends are involved in such adhesions. Moreover, the adhesions may be so secure that the chromosome ends become altogether obscured as in Figure 6, where there is no visible separation between end A2 and the end of chromosome *B*. Because of this high incidence of terminal adhesions in the salivary gland nuclei of *reynoldsi*, it is not possible to determine whether configurations like those in Figures *2B*, *2C* and 3 represent only a partial transverse separation in chromosome *C* or whether they are to be interpreted as terminal adhesions formed after the transverse separation has occurred. In view of this unusual behavior of the *reynoldsi C*, it was not possible for Rohm to determine which two of the four "ends" correspond to the true ends of the intact germ line chromosome. Consequently, in constructing theoretical evolutionary schemes, she had to select arbitrarily for the *reynoldsi* chromosome a sequence of segments. In her first interpretation (chromosomal inversion) she assumed C1 and C4 to be terminal, and in the alternative scheme (chromosomal transposition) C2 and C4 were taken as the true chromosome ends. Representing the *ocellaris* and *reynoldsi* homologues as shown in diagram 2. Rohm's proposals can be outlined in the manner shown in Diagrams 3 and 4.

The *reynoldsi* sequence can be derived from the *ocellaris* standard by two successive inversions and the concomitant loss of the terminal region A1a-A1c, the first inversion involving breaks at loci A1c and C5e and the second inversion involving breaks at A4a and A1c. Representing the points of break by a colon (:) and the deficient tip region by an asterisk (*), this phylogeny can be constructed as shown below in Diagram 3.

In the *reynoldsi* sequence thus derived, C1 and C4 are considered to be the true chromosome ends, and the transverse separation during development occurs between C2 (locus A4b) and C3 (locus A1c).

On the alternative interpretation, the *reynoldsi* chromosome is derived from the *ocellaris* standard by means of a single transposition with breaks at A1c, A4a, and C5e and the concomitant loss of the tip region A1a-A1c. (Diagram 4.) In this derivation C2 and C4 are assumed to be terminal.

A New Phylogeny

On the basis of new evidence it is now possible to demonstrate that neither of the *reynoldsi* sequences selected by Rohm is the correct one. Instead, C1 and C3 correspond to the ends of the intact germ line chromosome, and the transverse separation during development occurs between C2 and C4. The evidence referred to is an X-ray induced rearrangement in *reynoldsi* involving a reciprocal translocation between chro-

Diagram 2.

(*oc*) END 1 A1a—A1c—A4a, A4b—C5e, D1a—D8f END 2

(*rey*) END 1 C5e—A4b, A1c—A4a, D1a—D8f END 4

Diagram 3.

(*oc*) END 1 A1a—:A1c—A4a, A4b—C5e:D1a—D8f END 2

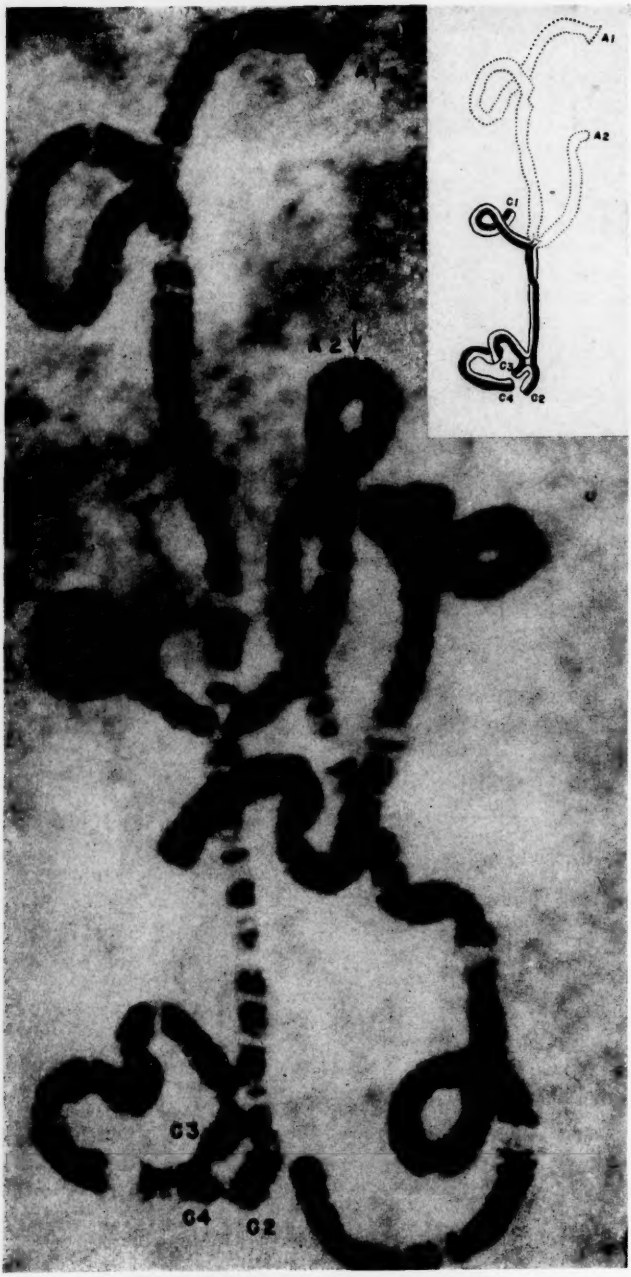
hypothetical intermediate * C5e—A4b:A4a—A1c:D1a—D8f

(*rey*) END 1 * C5e—A4b, A1c—A4a, D1a—D8f END 4

Diagram 4.

(*oc*) END 1 A1a—:A1c—A4a:A4b—C5e:D1a—D8f END 2

(*rey*) END 2 * A4b—C5e, A1c—A4a, D1a—D8f END 4



TRANSLOCATION AND INVERSION

Figure 6

Photomicrograph and camera lucida drawing of X-ray induced translocation (chromosomes *A* and *C*) and inversion (chromosome *C*) in *S. reynoldsi* (heterozygous state). In the drawing the normal chromosome *C* is represented in solid black, the rearranged *C* in outline, and chromo-

(Continued on next page)

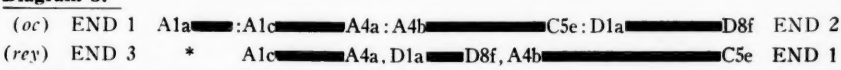
mosomes *A* and *C* and an inversion within *C*. This rearrangement, as observed in the heterozygous condition, is shown in Figures 6 and 7*A*. Upon examination of the photomicrographs and their respective outline drawings, it is found that C1 and C3 are terminally located. In both figures, moreover, the transverse separation has occurred, and C2 and C4 are clearly identifiable; the point of separation is located within the inversion loop. In view of the fact that the germ line (sperm) chromosome *C* on which the X-rays acted was intact (no transverse separation) at the time of irradiation, it can be concluded that C1 and C3 correspond to the true ends of the mitotic chromosome. A stock of flies heterozygous for this induced rearrangement was established and kept for at least six months. During that interval the inversion and translocation were separated by means of crossing-over. There was no obvious alteration in phenotype associated with either aberration.

The derivation of the *reynoldsi* chromosome from the *ocellaris* standard by means of inversions involves more steps than either of the sequences considered by Rohm. It is theoretically possible to get from the *ocellaris* to the *reynoldsi* condition in one step: by a transposition of chromosome material and the concomitant loss of the A1a-A1c tip region, with breaks occurring at A1c, A4a, and D1a as is shown below in Diagram 5. Actually, however, on the basis of the extensive studies on *Drosophila* and the preliminary studies on *Sciara*, there is no precedent for the occurrence of natural chromosomal transpositions. But there is considerable evidence to support the alternative inversion hypothesis. Repeatedly in *Drosophila*, where predicted intermediate chromosomal arrangements have been found, the process of inversion as the primary mechanism of gross evolutionary change has been upheld. And in *Sciara* the case for alteration by inversions becomes increasingly strong. It is to be recalled that both Carson and McCarthy, in studies on wild populations of *Sciara*, found numerous inversions. Moreover, in the construction of unidirectional gene sequence phylogenies for the chromosomes of *S. impatiens*, Carson discovered the gross changes in *A* and *C* to be clearly related as included inversions, some of these inversions being cytologically terminal. Even more significant for our discussion, Rohm observed in an intraspecific hybrid of *ocellaris* a short intercalary inversion near end 2 of chromosome *C*.

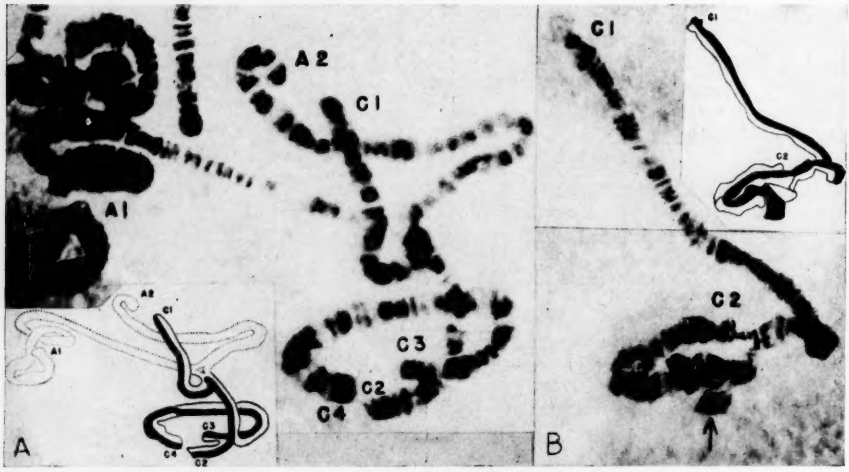
A Terminal Inversion

There is additional new evidence to support the inversion hypothesis, namely, the occurrence within a different intraspecific *ocellaris* hybrid of a natural inversion involving approximately one-third the entire length of *C* and including the terminal bands on end 2 (Figure 7*B*). This rearrangement is of interest not only because it supports generally the inversion hypothesis under consideration but also because it is *terminal*. By virtue of its terminal nature it merits

Diagram 5.



some *A* by a dotted line. The point of translocation and the point of inversion are both within segment 1-2, the former being approximately midway between *C1* and *C2*, and the point of inversion being very near *C2*. There is some sticky material which joins *C2*, *C4*, and *C3*, but the separation between *C2* and *C4* can be seen. The "crown" near *C4* is very conspicuous; the "bulb" near *C2* is not very evident, probably because this region of the chromosome has been prevented from stretching by the inversion configuration. The inversion loop includes practically the whole 3-4 segment and a short part of 1-2 (near *C2*). Chromosome *B* is shown in the photograph but not in the drawing. It is stuck to end *A2*, the point of adhesion is indicated by the arrow. This rearrangement figure demonstrates that *C1* and *C3* are terminal, *C2* and *C4* being interstitial.



INDUCED AND NATURAL REARRANGEMENTS

Figure 7

A—Same as Figure 6 except that end *A2* lies free in the nucleus. *B*—A natural terminal inversion on chromosome *C* observed in the salivary gland nuclei of an interspecific *ocellaris* and *reynoldsi* hybrid. The inverted homologue is represented in solid black, the normal chromosome in outline. The arrow indicates the new end of the inverted chromosome. For the point of break on the normal *ocellaris* chromosome see Figure 2*A*. Compare end *C2* in this Figure and in Figure 2*A* and note that the bands most terminally located have been inverted.

consideration on two counts. First, such alterations which appear to involve only one chromosome break, have rarely been reported for *Drosophila* and most other organisms. Three terminal inversions were found by Carson[1] in *S. impatiens*, thereby making the frequency of such changes in this genus unusually high (see Carson, pp. 34-35 for discussion of this situation). In the second place, the derivation of the *reynoldsi C* from the *ocellaris* standard by means of inversions involves the rotation of a terminal segment of the *ocellaris* chromosome. Consequently, it is very important to demonstrate that cytologically terminal material *can* be inverted in this species.

There is no particular value in constructing all the chromosome *C* phylogenies which are theoretically possible, since none of the hypothetical intermediates has been found. Suffice it to demonstrate how Rohm's inversion scheme would have to be supplemented by a terminal inversion with a break at locus A4b in order to produce the correct *reynoldsi* sequence. (Diagram 6.)

The transverse separation in the *reynoldsi* chromosome occurs between loci A4b and D8f, thereby creating two approximately equal segments. This

Diagram. 6

(*oc*) END 1	A1a—:A1c—	A4a, A4b—	C5e : D1a— D8f END 2
hypothetical intermediate	*	C5e—	A4b : A4a— A1c : D1a— D8f
Rohm's sequence END 1	*	C5e—	A4b : A1c— A4a, D1a— D8f END 4
correct (*rey*) END 1	*	C5e—	A4b, D8f— D1a, A4a— A1c END 3

equality in length, plus the median location of the centromere on the mitotic chromosome, would lead one to suspect that the banded element is pulling apart at the centromere region. Other V-shaped chromosomes in *Sciara*, however, including the V-shaped *C* in *ocellaris*, do not exhibit this unusual behavior in the salivary gland nuclei. There is a plausible explanation of the discrepancy, but it is entirely speculative. If the *reynoldsi* C has been derived from the *ocellaris* standard by inversion, then there is one important difference between the *reynoldsi C* and the V-shaped *ocellaris* homologue, namely, the rotation of terminal material to an intercalary position. Moreover, if the hypothetical antecedent of the *reynoldsi C* had a median centromere and if the terminal inversion were accomplished in the manner diagrammed above, then the end region (locus D8f) would have been brought immediately adjacent to the centromere. And such close proximity might possibly lead to the peculiar behavior observed in the *reynoldsi C*.

This speculation emphasizes the importance of determining (1) whether the *reynoldsi C* was derived from a rod- or V-shaped chromosome, and (2) the location of the centromere on the banded chromosome *C* in *ocellaris*.

Relationship of Rod and V Chromosomes

It has already been pointed out several times that in some strains (unisexual) of *ocellaris*, chromosome *C* at metaphase is a rod and in other (bisexual) strains it is V-shaped. The strains of *ocellaris* are all interfertile, and no isolating mechanisms have been detected. *Reynoldsi* and *ocellaris* can be crossed and an F_1 hybrid obtained; but, in making the interspecific mating, *ocellaris* females and *reynoldsi* males have to be bred. The reciprocal cross yields no offspring. Females from either unisexual or bisexual strains of *ocellaris* can be used in the hybrid cross, but so far as the mechanism of sex determination is concerned, *reynoldsi* is much more closely related to the bisexual strains (V-shaped *C*) of *ocellaris* than to the unisexual (rod-shaped *C*) ones.[2] Every strain of *reynoldsi* studied to date has been bisexual. In view of this fact, it appears that *reynoldsi* is a derivative of bisexual *ocellaris* (or *vice versa*). Most likely, therefore, the *reynoldsi C* originated from a chromosome which had a median centromere.

To localize the centromere regions on the salivary gland chromosomes of *Sciara* is very difficult. There is no chromocenter in this genus, the banded chromosomes lie practically free in the nucleus, and the centromeres cannot be identified as such. Consequently, these regions can be located only within rather wide limits. For instance, it can be determined that the centromere on the rod-like *C* of *ocellaris* lies at end C1 and not at end C2. This determination is made on the basis of an X-ray induced translocation between chromosomes *X* and *C* (Figure 5*B*). From previous studies on reciprocal translocations[3], the centromere of the rod-shaped *X* is known to lie at end X1 of the salivary gland chromosome. Since dicentric and acentric chromosomes do not maintain themselves normally at cell division, each of the translocation chromosomes in Figure 5*B* must have one centromere only. The rearranged chromosome ending in X1 carries the centromere of *X*; consequently, the *C* centromere must be located on the *C1-X2* translocation chromosome. This means, then, that the centromere of *C* is located within the short C1 arm of the translocation cross in Figure 5*B*. To place the centromere in strains of *ocellaris* with a V-shaped chromosome *C* is more difficult; on the basis of the evidence at hand this determination cannot as yet be made. Only this do we know: that in passing from the rod to the V, there has been no gross rearrangement of material; only the centromere proper seems to have shifted.[2]

Summary and Conclusions

1. In the salivary gland nuclei of *S. reynoldsi*, chromosome *C* is represented

by two approximately equal segments. On the basis of new evidence the proper sequence of these segments has been determined. C1 and C3 correspond to the ends of the intact mitotic chromosome.

2. Since C1 and C3 are terminal, both of Rohm's evolutionary schemes for the derivation of the *reynoldsi C* from the *ocellaris* standard have to be revised.

3. The *reynoldsi* sequence *can* be derived from the *ocellaris* standard by a single chromosomal transposition, but there is no evidence to support rearrangement by intrachromosomal transposition in this genus.

4. The discovery of a long terminal (End 2) inversion in chromosome *C* of an intraspecific *ocellaris* hybrid supports Rohm's hypothesis that inversion has played an important part in the evolutionary changes in chromosome *C*. This particular inversion is of considerable significance, because it demonstrates that cytologically terminal material *can* be inverted in *ocellaris*. And the inversion of a terminal segment of chromosome has to be invoked in any evolutionary scheme which derives the *reynoldsi* sequence by means of inversions.

5. In those strains of *ocellaris* which have a rod-shaped mitotic *C*, the centromere is located near end C1 of the salivary gland chromosome. It has not been located on the banded element in those strains with a V-shaped *C*. In *reynoldsi*, where the centromere is regularly median in position, the point of separation in the salivary gland chromosome is believed to be adjacent to the centromere region. The cause of this transverse separation is not known, but it is suggested that the approximation of cytologically terminal material to the vicinity of the centromere may be responsible.

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DESTRUCTION OF THE ROSCOE B. JACKSON MEMORIAL LABORATORY

THE fire which swept the Jackson Memorial Laboratory on October 23 burned or suffocated all but a handful of the hundreds of thousands of mice which made this mouse metropolis a unique outpost in the fight against cancer. The loss is estimated at half million dollars for plant and equipment, only a fraction of which was covered by insurance. Plans to rebuild on the present site are being completed, and in the interval the Laboratory is operating from the Hamilton Station, located about three miles from the main Laboratory, and not touched by the fire. One of the buildings was not burned, but the mice suffocated. The Library and most of the equipment anl records were destroyed.

The Damon Runyon Cancer Fund has announced an initial grant of $50,000 toward rebuilding the Laboratory, and a committee to raise additional funds for this purpose is in process of formation. In addition to funds for rebuilding two other things are urgtntly needed: (1) Pertinent publications (reprints, books, and miscellaneous publications) in the fields of genetics, embryology, physiology, etc.: and (2) mice of known Jackson ancestry to rebuild the colony. The Laboratory supplied its standardized strains of mice to hundreds of research projects in cancer and related subjects. Hence, there is a very urgent need to make available again as soon as possible all of the important Jackson Laboratory strains. Those who can assist by furnishing breeding stock to reestablish these strains are urged to get in touch with the Laboratory as soon as possible. Address: Box 78, Bar Harbor, Maine. Contributions of literature can be sent to the same address, care of Dr. Hummel, Chairman of the Library Committee of the Laboratory.

GENETICS CONGRESS TRAVEL PLANS

A Report from Miss Mary Laughlin

HAVING just returned fom nine months in Europe, I am anxious to pass on to prospective members of the Eighth International Congress of Genetics information which may be helpful in planning pre-Congress and post-Congress travel.

Transportation in Sweden, in fact in all three Scandinavian countries, is as satisfactory as in prewar times. Hotel space never was adequate for the host of visitors who wanted to see Scandinavia, and of course there is less now than there was in 1939. So for that reason, I advise all Congress members who expect to travel before or after the Congress to make their plans early. The Clara Laughlin Agency, which is official Travel Agent for the Congress is planning several trips about which detailed information wil be available shortly.

There are several possibilities for interesting trips. Those who plan to arrive in Sweden the week before the Congress opens may like to join the week's motor trip from Gothenburg through the agricultural and chateau district of Skane, in the south, where you will find as many beautiful and interesting chateaux as there are on the Loire in France. Furthermore, they are not as well known to Americans. We understand that special exhibits of interest to the Congress members will be shown at the great agricultural experimental station at Svälov in Skane, so we are routing this trip to include these, on the way from Gothenburg to Hälsingborg, along with the fine school at Alnarp where scientific farming is taught. Incidentally, the finest horses in Sweden are bred at some of these old chateaux to be visited on this trip. Special arrangements will be made to see all places of interest to tour members. The trip will continue north from Malmö to Jönköping, home of the Swedish match industry, to Gränna on Lake Vättern (Lakes Vättern and Vänern are the largest inland bodies of water in Europe outside of Russia), and along the side of the most beautiful part of the Göta Canal on the south side to the Berg Locks and up to Linköping and in Stockholm.

The same trip will be available going south from Stockholm as a post-congress trip, continuing from Malmö over to Copenhagen and down the Continent to Amsterdam by rail. Thence to the Hague by motor, with a detour to Bastogne, scene of the Battle of the Bulge, it desired. Paris and London will finish this particular trip. For those who wish to visit Switzerland an extension will be made from Brussels to Bâsle and a week's tour will be offered to reach Lucerne on August 1st. This is Swiss Independence Day when traditional costumes are worn and much local excitement adds to the color and the natural beauty of that lovely town lying on the shores of Lake Lucerne under the majesty of Mount Pilatus and the Rigi.

For those who want to see more of Scandinavia after the Congress, we have planned a two week's trip from Stockholm, going north to the lovely district of Rättivik, Leksand and Mora where local costumes are still worn to church of a Sunday morning. And thence by motor through the Gosta Björling country to Karlstad on Lake Vänern. This was John Ericsson's birthplace. This is the center of the lumber industry of Sweden, one of her greatest natural resources, since her forests cover more than half of her entire area. Then on to Oslo by rail, after which a week's motor and boat trip combined will be taken starting at Aandelsnes, half way up the Norwegian coast, down through the fjords and mountains and glaciers of Merok, Groetli, Balholm, Gudvangen, Stalheim and Voss to Bergen. There will be a return sailing from Gothenberg offered on July 30th. For those who wish to have an English extension there will be a trip to Newcastle from Bergen on the B. and N. Line. And so home!

These are the most interesting possibilities for post-congress traveling. Certain members will wish to be in Paris by the 21st of July to attend the 13th International Congress of Zoology in which case direct connections from Sweden to Paris will be arranged. There is a direct bus line from Stockholm to Paris, which will give an excellent opportunity to see the country at reasonable cost. We urge that all members select the trips they desire to make as soon as the itineraries are available because a prompt decision is essential to insure that reservations are made in time.

At present the prospects of travel in Germany are not very good. Special tours, limited to a few people, with objectives approved by the State Department may possibly be arranged. Any who might contemplate such a trip, should get in touch with us at once.

In closing I should like to advise that the Clara E. Laughlin guidebook, "So You're Going to Scandinavia" will be off the press early next spring, completely revised and brought up to date for post-war travel. It covers travel in all three countries and is written from the historic and artistic point of view. It will be helpful and enjoyable reading before leaving home and useful as a daily "on the spot" guide and companion. It is very important that all members of the Congress make their travel plans at the earliest possible moment. Address inquiries to the Clara Laughlin Travel Agency, 38 E. 57th St., New York City 22, N. Y.

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The world literature on agriculture, forestry and related sciences may be followed through the publications of this organization. In addition to the Technical Communications listed below, the I.A.B. publishes abstracting journals covering entomology, mycology, agricultural parasitology (helminthology), soil science and the use of fertilizers, animal health, animal nutrition, animal breeding and genetics, dairy science, plant breeding and genetics, horticulture and plantation crops, grassland husbandry and fodder production, and forestry.

RECENT TECHNICAL COMMUNICATIONS

THE NEW GENETICS IN THE SOVIET UNION. By P. S. Hudson and R. H. Richens. 1946. 6s. An objective review of the "genetics controversy."

THE USE OF HETEROSIS IN THE PRODUCTION OF AGRICULTURAL AND HORTICULTURAL CROPS. 1946. 3s. A review of papers which have a bearing on the commercial exploitation of hybrid vigour.

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THE USE OF AERIAL SURVEY IN FORESTRY AND AGRICULTURE. 1947. 7s.6d. Recent developments and methods. factors affecting efficiency and cost, and examples of application to various problems and methods of land-use survey.

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